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Herman Singh Bagga, Thomas Chi, Joe Miller, and Marshall L. Stoller

The pathophysiology of the various forms of urinary stone disease remains a complex topic. Epidemiologic research and the study of urine and serum chemistries have created an abundance of data to help drive the formulation of pathophysiologic theories. This article addresses the associations of urinary stone disease with hypertension, cardiovascular disease, atherosclerosis, obesity, dyslipidemia, diabetes, and other disease states. Findings regarding the impact of dietary calcium and the formation of Randall's plaques are also explored and their implications discussed. Finally, further avenues of research are explored, including genetic analyses and the use of animal models of urinary stone disease.

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David S. Goldfarb and Omotayo Arowojolu

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Brian H. Eisner, David S. Goldfarb, and Gyan Pareek

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Michael E. Lipkin and Glenn M. Preminger

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Foreword



Samir S. Taneja, MD
Consulting Editor

Dating back to the days of traveling barbers treating bladder stones to the modern era of endourology, stone disease is, perhaps, the longest standing staple of urologic practice. With the advent of imaging, the number of urinary stones seen in practice grew to include asymptomatic stones for which treatment may or may not be indicated. Advances in imaging now offer insight into stone composition, in addition to accurate measurements of size and position.

In the contemporary era, the urologist's role is no longer to simply crush and remove, but instead, to treat the acute sequelae of stone passage, determine the necessity for treating the asymptomatic stone, and provide evaluation and management for the prevention of stone formation. In this regard, the management of stone disease represents one of the best examples of multidisciplinary care in Urology. As we move forward into the era of disease-based multidisciplinary approaches to health care, we can learn a great deal from the paradigms for care established by our colleagues who have chosen to specialize in the management of urinary stones.

In keeping with our goal of using *Urologic Clinics* as a means of demonstrating multidisciplinary approaches to urologic disease, this issue, guest edited by my colleague Ojas Shah, is constructed to review the comprehensive approach to the stone patient. Dr Shah has done a wonderful job of including current, relevant topics and inviting leading authorities within the discipline to contribute

their perspective. The articles included range from surgical therapy to metabolic evaluation to dietary manipulation to cost-effectiveness in stone management. We are deeply indebted to each of the authors for their outstanding additions to this monograph.

In reviewing the content of this issue of *Urologic Clinics* I sincerely hope that you will gain insight into an aspect of stone disease management that you had previously not considered. Since most urologists treat stones surgically, it remains important for us as a urologic community to have a comprehensive understanding of the basis of stone formation, an evaluation of the metabolic derangements leading to stone disease, and the necessary preventive measures needed for the individual patient. In doing so, we will be well poised to provide complete care as the health care system evolves. Once again, I am deeply indebted to Dr Shah and all the contributing authors for a fabulous issue of *Urologic Clinics*.

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Preface



Ojas Shah, MD
Guest Editor

Upper urinary tract stones, which affect a large proportion of our population, are a significant source of morbidity and cost. With numerous risk factors, strategies to reduce stone recurrence and to minimize the need for surgical stone treatment are essential. Furthermore, a thorough understanding of the pathogenesis and pathophysiology of urolithiasis is critical in understanding the process for prevention. This issue of the *Urologic Clinics* provides new insights into kidney stone formation and the metabolic evaluation of first-time and recurrent stone formers to decrease stone recurrence.

In addition to medical therapy to decrease stone recurrence and aid in stone expulsion, the latest dietary and alternative therapy recommendations for stone prevention are discussed.

Over the last several years, new options in the diagnosis of stone disease have become available as well as strategies to optimize the older technologies. This issue updates the practitioner on the imaging techniques for urolithiasis, while providing the most up-to-date information on methods to reduce radiation exposure. Additionally, stone characterization with imaging is discussed, which has enhanced treatment outcomes by helping choose the most appropriate management based on stone size, location, density, and composition.

Despite efforts for stone prevention, stones continue to occur. Therefore, surgical treatments with the least morbidity and highest effectiveness are being investigated to optimize outcomes. Although shockwave lithotripsy technology has not advanced significantly in many years, new techniques involving acoustic coupling, shockwave rate, and shockwave energy sequence have led to improved outcomes. This issue also discusses new innovations in the minimally invasive surgical modalities of ureteroscopy and percutaneous renal

surgery that has led to reduced morbidity and overall improved efficacy. The emerging role of laparoscopy and robotics in the setting of complex stone disease is also addressed. Additionally, management of stones in complex situations such as pregnancy, kidney transplantation, and anomalous kidney anatomy is discussed thoroughly.

In the new world of health care economics, in addition to the emphasis of investigating and improving the quality of life of stone formers, the treatment of stone disease is addressed from a cost-effectiveness perspective. This allows practitioners to develop treatment strategies that maximize success and stone-free rates with the minimal amount of procedures. One new and important concept also addressed in this edition is the impact of stone disease recurrence and treatment on the development of chronic kidney disease.

As the guest editor of this issue, I made it my goal to provide the reader with a valuable, comprehensive resource that familiarizes them with the current concepts and decision-making thought processes that have evolved in the multidisciplinary management of urolithiasis. I am extremely thankful for the hard work of the contributors to this issue. As recognized leaders in this field, their time and effort are appreciated and their insights are invaluable.

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New Insights Into the Pathogenesis of Renal Calculi

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Joe Miller, MD, Marshall L. Stoller, MD

KEYWORDS

• Genitourinary system • Urinary calculi • Etiology • Review • Calcium

KEY POINTS

- Epidemiologic research and the study of urine and serum chemistries have created an abundance of data to help drive the formulation of pathophysiologic theories of stone formation.
- The abundance of associations between nephrolithiasis and metabolic disease states forces us to reconsider existing hypotheses of stone formation, including the etiology of Randall's plaques.
- Future steps in understanding the pathophysiology of urinary stone disease will likely include genetic studies and the use of animal models.

INTRODUCTION

Urolithiasis has been a documented medical affliction since at least ancient Egyptian civilization,¹ and continues to be responsible for an increasing number of practitioner visits worldwide.^{2,3} Furthermore, the recurrence rates of symptomatic stones are high at more than 50% within 5 years of a first episode,⁴ suggesting that identifiable high-risk cohorts may experience common pathways in the pathogenesis of stone formation that can be targeted for prevention efforts. This exciting field of research continues to grow. The goal of this article is to discuss new frontiers of understanding regarding the pathophysiology of urinary stone disease.

PHYSIOCHEMICAL ASPECTS OF URINARY STONE FORMATION

At the root of the pathophysiology of urolithiasis is the physiochemical formation of urinary stones. As the glomerular filtrate passes through the nephron, the urine becomes concentrated with stone-forming salts which, when supersaturated, can precipitate out of solution into crystals that can either be expelled with voided urine or grow and

aggregate under the relative influences of various stone-promoting or stone-inhibiting agents, resulting in stone formation.⁵ Given an estimated transit time through the nephron of 5 to 7 minutes, traditional thought was that this did not allow sufficient time for free particles to aggregate enough to increase in size to occlude a tubular lumen and serve as a site of stone formation.⁶ This theory suggested that some adhesion to tubular epithelial cells as fixed particles would be required to allow for crystal growth and subsequent stone formation. Although recalculation of nephron dimensions in the context of crystal conglomeration during acute increases in supersaturation have concluded that a free-particle theory of stone formation is a potential mechanism of disease,⁷ research into the fixed particle mechanism has gained some favorable results. In particular, the theory has been evaluated that intraluminal deposits, mostly within the distal nephron, could serve as sites of stone formation.

Histopathologic evidence of plugs of mineral deposits has been noted in several stone-forming groups of patients, such as those with brushite stones, hyperparathyroidism, cystinuria, and distal renal tubular acidosis, and those with a history of intestinal surgery, including bypass surgery for obesity, small bowel resection, and ileostomy

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creation. This theory is supported by observations of stone material growing from the ends of these plugs; however, whether these intraluminal deposits lead to stone formation remains unknown. Much research must be performed to elucidate this question, and most likely this is one of multiple pathways in the pathogenesis of urinary stone disease.^{8,9}

RANDALL PLAQUES

Associations with Urinary Stone Disease

In contrast to the free and fixed particle theories of stone pathogenesis is the Randall plaque hypothesis. The theory evolved during a search for an initiating lesion for renal stones, which Alexander Randall thought originated in the renal papilla. Strong evidence was gained for this hypothesis during human autopsy studies in which calcium deposits were found in nearly 20% of renal papillae, with nearly one-third of these patients having a primary renal stone at the site. These deposits were coined "Randall plaques" and histologic analysis showed that the lesions were in the interstitial tissues of the papilla near segments of the nephron, rather than within the nephron lumen itself. Randall hypothesized the exposed plaque material served as a nidus for stone formation.^{10,11} This hypothesis has regained popularity over the past decade, particularly in regard to the pathogenesis of idiopathic calcium oxalate stones, the most commonly encountered stone in clinical practice. Published observations by Miller and colleagues¹² during endoscopy confirmed that most stones in their study population of patients with idiopathic calcium oxalate stones, which were visually noted to be attached to and primarily originating from these Randall plaques (Fig. 1). Further evaluation from this group lent more credence to this observation. The group decided to also analyze free-floating stones encountered during ureteroscopy. More than half of these stones had mucus-covered, concavely cupped regions on one side of the stone that were found to contain apatite on micro-CT analysis of internal structure. This evidence supported the idea that these stones had also grown from a papillary plaque and then subsequently fallen off. Internal structure analysis of the remainder of the stones showed similar evidence of previous attachment to a Randall plaque at one end indicated by the presence of apatite. This finding also provided strong evidence that calcium oxalate stones arise from Randall plaques.¹³

Formation Theories

The origin of Randall plaques themselves remains an issue of debate. On histopathologic examination

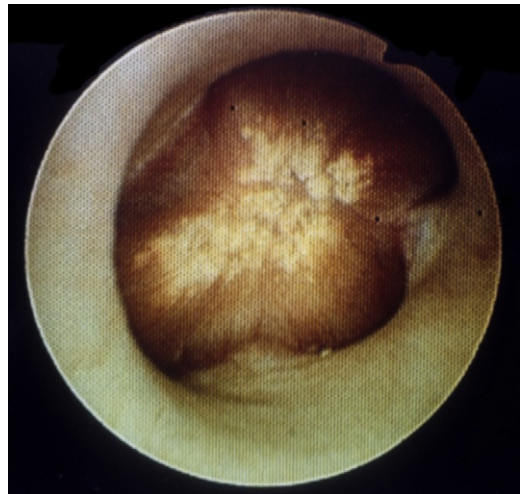


Fig. 1. A Randall plaque forming at a renal papilla, as visualized on endoscopy. No stone is currently attached.

of the lesions, Evan and colleagues¹⁴ suggested that these plaques arise from the basement membrane of the thin loops of Henle and subsequently protrude into the epithelium of the renal papillae after expanding through the interstitium. This theory has been based on examination of renal papillae from patients with idiopathic calcium oxalate stone formation. Using light microscopic analysis, the group first confirmed that Randall's plaques were limited only to the papillary interstitium and did not reside within the renal tubule, and then examined regions with limited versus heavy plaque burden to identify patterns of progression.¹⁴ In separate studies, they have also noted small deposits within the basement membrane of the thin loops of Henle containing varying numbers of ring-like layers of proteins, suggesting the origin of stones to be within the basement membrane itself.^{15,16}

Other analyses of Randall plaques from cadaveric samples with radiographic and immunohistochemical analysis, however, have noted the plaques to extend deep into the papilla, into the basement membrane of the collecting tubules and the vasa recta.¹⁷ These observations have led to a vascular theory of Randall plaque formation and subsequent calcium oxalate stone development, which suggests that repair of injured papillary vasculature in an atherosclerotic-like fashion results in calcification near vessel walls that eventually erodes a calculus into the papilla through the renal papillary interstitium.

The vascular theory of Randall plaque formation is supported by 3 properties of renal physiology. The first is based on the idea that areas of turbulent flow are predisposed to inflammation and

atherosclerosis. In the case of arterial plaques these locations include the bifurcation of the aorta, iliac arteries, and carotid arteries.¹⁸ Laminar blood flow changes to turbulent flow at the tip of the renal papilla because of a 180° transition, likely predisposing the area to atherosclerotic-like reactions and subsequent plaque formation. Secondly, a 10-fold or higher increase in osmolality occurs between the renal cortex and the tip of the papilla.¹⁹ In this hyperosmolar microenvironment, resident inflammatory cytokines and proteins can accumulate and promote plaque aggregation in response to vascular injury. Lastly, a decreasing gradient of oxygen-carrying capacity occurs from the renal cortex to the tip of the papilla.²⁰ In severe cases, as with diabetes mellitus, this can translate to events such as papillary necrosis and sloughed papillae that may obstruct the ureter and create a microenvironment of inflammation. These 3 factors can promote an atherosclerotic-like response to inflammation with perivascular calcification, which may lead to Randall plaque formation.

Given a known association of esterified cholesterol with atherosclerotic processes, this vascular theory was investigated with cholesterol extraction studies on calcium oxalate stones. Analysis noted high esterified-to-free cholesterol ratios in stones with high calcium oxalate composition, providing some support for this hypothesis.²¹ Indirect evidence of the interaction between the vascular system and urinary stone formation has also been noted after the interesting finding that urinary stones tend to be largely unilateral and on the dependent sleeping side of patients.²² These observations prompted renal perfusion studies of patients in various sleep positions, with results noting that renal perfusion is also position-dependent. Increased renal blood flow on the dependent sleeping side of patients may lead to increased turbulence and accumulation of inflammatory elements contributing to a vascular event leading to urinary stone formation.²³ This association may implicate increased renal blood flow as a contributory cause of urinary stone disease. This mechanism may work in concert with hyperfiltration, leading to increased solute deposition and subsequent accumulation of stone-forming elements. These observations open the doorway to explore the associations between vascular disease and urolithiasis.

VASCULAR DISEASE ASSOCIATIONS WITH UROLITHIASIS

To explore new frontiers in the pathogenesis of urinary stone disease, it is helpful to explore

associations between urolithiasis and other phenomena, such as vascular disease. The link between urolithiasis and vascular disease is well documented in the literature. Nephrolithiasis has been associated with a 31% increased risk of myocardial infarction (MI), as documented by Rule and colleagues²⁴ in a study of more than 4500 stone formers compared with nearly 11,000 control patients with 9 years of follow-up. The risk was noted to be independent of kidney disease or other common risk factors for MI. Data from a large cohort of nearly 10,000 women participating in the Study of Osteoporotic Fractures has similarly revealed that patients with a history of nephrolithiasis have an increased relative risk (RR) of MI (RR, 1.78) and angina (RR, 1.63).²⁵

Although the precise mechanisms underlying these associations remain to be elucidated, one speculation is that the disease processes may have shared risk factors that have not been fully identified. One potential risk factor could be atherosclerosis, as supported by the vascular theory of Randall plaque formation. The association between nephrolithiasis and subclinical atherosclerosis was recently investigated within the Coronary Adult Risk Development in Young Adults (CARDIA) cohort, which identified a significant association between kidney stones and carotid artery atherosclerosis (odds ratio [OR], 1.6), even after adjusting for known major atherosclerotic risk factors. This study provided further support for possible common systemic pathophysiology that may be shared between vascular and urinary stone disease.²⁶

Perhaps most well studied is the association between urinary stone disease and hypertension, which was recognized as early as the 1760s when Morgagni described a patient with clinical and anatomic findings suggestive of both diseases.²⁷ More recent studies have confirmed these observations. In their prospective analysis of 503 men, Cappuccio and colleagues²⁷ noted an RR of 1.96 for the development of kidney stones in hypertensive men compared with normotensive men at 8 years. Similarly, in another prospective analysis, Borghi and colleagues²⁸ noted an OR of 5.5 linking a baseline history of hypertension to the formation of a kidney stone at 5 years of follow-up. This risk seemed particularly pronounced for individuals who were overweight. The link between hypertension and urinary stone disease seems to be potentially bidirectional, as supported by studies that have demonstrated stone formation to predate the onset of hypertension. In their prospective study of a cohort of more than 50,000 men, Madore and colleagues²⁹ noted an association between

nephrolithiasis and risk of hypertension (OR, 1.31), and reported that in men who had both disorders, 79.5% experienced the occurrence of nephrolithiasis before or concomitant to their diagnosis of hypertension. A similar association was seen in women, with an RR of 1.36 for developing a new diagnosis of hypertension in those with a history of nephrolithiasis, as demonstrated from data secured from the Nurses' Health study, a cohort with nearly 90,000 women.³⁰

Although an association seems to exist between hypertension and urinary stone disease, the pathophysiology responsible for this link remains unclear. Multiple theories have been proposed, some highlighting the contribution of urinary composition to the mechanism of disease. Strazzullo and colleagues³¹ in a case-controlled study of 110 patients, evaluated calcium metabolism in cohorts with and without essential hypertension, noting higher urinary calcium excretion rates in hypertensive individuals despite similar total and ionized serum calcium levels. The response to intravenous calcium infusion was also investigated, showing that hypertensive patients excreted more calcium at all serum calcium concentrations, suggesting that a form of urinary leak of calcium could be occurring within hypertensive patients. Cappuccio and colleagues³² similarly recorded abnormalities of calcium metabolism in hypertensive patients, specifically highlighting increased parathyroid gland activity, urinary cyclic AMP, and intestinal calcium absorption. Increased levels of urinary uric acid³³ and decreased levels of urinary citrate³⁴ have also been seen in studies of hypertensive individuals. These risk factors for the development of urinary stones are well established.^{35,36} Differences in urinary composition of magnesium and oxalate may also contribute to the link between hypertension and urinary stone disease.²⁸ Diet has also been implicated as a potential link between hypertension and a predisposition for urolithiasis. In particular, the known effects of increased dietary sodium, known to promote urolithiasis via hypercalciuria³⁷ and also promote hypertension,³⁸ has led to its consideration as a potential parsimonious factor.

Animal models have also demonstrated this association between hypertension and urinary stone disease. Although otherwise rare in animals, Wexler and McMurtry³⁹ showed that strains of spontaneously hypertensive rats that were born normotensive and developed hypertension with maturation were prone to the development of urinary stone disease. The substrain most prone to urolithiasis also became obese with maturity and stereotypically formed microscopic stones

within the kidney. These stones began in a subepithelial location before detaching and serving as a nidus for further stone growth, a mechanism reminiscent of current Randall plaque theories of stone formation. This finding also implicates other metabolic associations with urinary stone disease, such as obesity.

OBESITY, DIABETES, AND URINARY STONE DISEASE

Several studies have found significant associations between weight and body mass index (BMI) and urinary stones. Taylor and colleagues,⁴⁰ in an analysis of 3 large prospective cohorts of nearly 250,000 individuals, showed that the RR of incident kidney stone formation for people weighing more than 100 kg, compared with those weighing less than 68.2 kg, was 1.44 in men, 1.89 in older women, and 1.92 in younger women. Using a BMI cutoff of 30, the RRs were 1.33, 1.90, and 2.09, respectively. Similarly, in a study of more than 800 renal stone formers, Del Valle and colleagues⁴¹ showed that most patients (nearly 60%) were either overweight or obese. In 2006, Taylor and Curhan⁴² investigated the relationship of BMI as a continuous variable to stone formation, and noted that even in nonobese patients (BMI <30), an increasing BMI lent itself to a higher risk of urolithiasis. The effect was most significant in women, wherein those with a BMI of 23 to 24.9 had a 25% increased incidence of stones compared with those with a BMI of 21 to 22.9. Those with a BMI of 27.5 to 29.9 had a 65% to 75% increased incidence. Similar results were seen in men, wherein those with a BMI of 25 to 29.9 had a 15% to 25% increase in stone incidence compared with those with a BMI of 21 to 22.9. These findings support the idea that increasing weight and BMI are directly correlated to susceptibility to urinary stone formation.

Multiple groups have investigated urine chemistries to better characterize the links between BMI and urinary stone disease. Ekeruo and colleagues,⁴³ for example, noted that obese (BMI >30) urinary stone formers most commonly had evidence of hypocitraturia (54%) and hyperuricosuria (43%) compared with nonobese stone formers. Taylor and Curhan⁴² and Powell and colleagues⁴⁴ similarly investigated urine chemistries, showing increased urinary excretion of oxalate, uric acid, phosphate, sodium, sulfate, and cysteine⁴⁴ in obese versus nonobese patients. Urinary composition in the obese population seems to contain higher levels of substances known to precipitate urinary stones compared with the nonobese population.

The close association between obesity and diabetes, another known risk factor for urolithiasis, may compound the influence of obesity on the development of urinary stones. Obesity has been shown to carry with it a well-established increased risk for diabetes mellitus.^{45,46} In several large-scale studies, patients with diabetes have been closely linked to increased risk of formation of all types of urinary calculi^{47,48} and increased risk of uric acid stone formation in particular.⁴⁹ Several pathophysiologic mechanisms have been suggested to explain these observations. One explanation offered by Canda and Isgoren⁵⁰ stems from their observation of decreased function of interstitial cells and neural tissue within the urothelial tissue of diabetic rabbits. They suggested that these perturbations of function could affect ureteral peristalsis and promote urinary stone formation by virtue of urinary stasis. Other authors, however, suggest that the insulin resistance seen in diabetics is the underlying mechanism through which stones form. Insulin resistance has been noted to impair renal ammoniogenesis, resulting in acidic urine. It also promotes reabsorption of uric acid in the proximal tubule, resulting in hyperuricemia. Both of these factors could contribute to an increased propensity for uric acid urolithiasis.⁵¹ Hyperglycemia has also been associated with increased urinary calcium⁵² and oxalate⁵³ excretion. Taken together, these metabolic changes may explain the consistent association seen between diabetes and urinary stone disease.

DYSLIPIDEMIA AND URINARY STONE DISEASE

The links between dyslipidemia and urinary stone disease have also been investigated. Kadlec and colleagues,⁵⁴ in their retrospective review of nearly 600 endourologic stone procedures for which stone composition data were available, noted that more than 30% of their cohort was characterized as dyslipidemic (defined by the use of a cholesterol-lowering medication). Of these patients with dyslipidemia, nearly 70% had calcium oxalate stones and 15% had uric acid stones. A recent study by Inci and colleagues⁵⁵ similarly found that total cholesterol levels were significantly higher in stone formers compared with patients who do not form stones, with the association noted to be particularly prominent for calcium oxalate and uric acid stone formers.

To evaluate the potential pathophysiologic mechanisms linking dyslipidemia with urinary stone disease, related research on atorvastatin may be useful to consider. Atorvastatin is a commonly prescribed drug used to decrease serum

cholesterol levels. Tsujihata and colleagues^{56,57} reported that the administration of atorvastatin to stone-forming rats significantly lowered crystalline deposits on quantitative light microscopy analysis of excised kidney specimens. They hypothesized that anti-inflammatory and antioxidative effects of the drug were responsible, through preventing renal tubular cell injury from oxalate and subsequently inhibiting renal crystal retention. In their experimental model, they found that urinary levels of biomarkers for renal tubular cell injury (*N*-acetyl glucosamidase) and oxidative stress (8-OHdG) were decreased significantly by atorvastatin treatment. Furthermore, atorvastatin treatment decreased the apoptosis of renal tubular cells. These results suggest that common pathophysiology shared between dyslipidemia and urinary stone formation may be related to inflammation and subsequent cellular injury of renal tubular cells.

THE METABOLIC SYNDROME AND UNIFICATION OF THE METABOLIC LINKS TO URINARY STONE DISEASE

Metabolic syndrome is the term given to a combination of risk factors that may include impaired fasting glucose, elevated blood pressure, central obesity, and dyslipidemia in the form of high serum triglycerides or low high-density lipoprotein cholesterol levels. The presence of at least 3 of these traits establishes a diagnosis.⁵⁸ This syndrome has been strongly associated with various disease states, most notably diabetes and cardiovascular disease, with a documented relative risk of 3 for diabetes, and 1.78 for cardiovascular disease and death.^{59,60}

More recently, metabolic syndrome has become the subject of increased urologic research because of continued observations that it is associated with an increased risk of urinary stone disease. West and colleagues⁶¹ examined the association between the number of metabolic syndrome traits and risk of nephrolithiasis using a national sample of patients in the United States. Prevalence of kidney stones increased with the number of traits, from 3% with 0 traits to 9.8% with 5 traits. The presence of 2 or more traits significantly increased the odds of stone disease, and the presence of 4 or more traits was associated with an approximate 2-fold increase. In a study of Italian adults, Rendina and colleagues⁶² similarly found an approximate 2-fold increase in the risk of stone disease for patients with metabolic syndrome. In an analysis of the individual components of the syndrome, they found that the only syndrome trait independently associated with increased stone risk on its own was

hypertension. The risk of nephrolithiasis with hypertension was reported with an OR of 2.1 for men and 4.9 for women. The presence of hypertension with any other trait of metabolic syndrome further increased the risk of urolithiasis, with an OR of 2.2 compared with those individuals with hypertension alone. Jeong and colleagues⁶³ confirmed a similar pattern in an American population, finding metabolic syndrome and the trait of hypertension as independent risk factors for the presence of urinary stones. The other components of metabolic syndrome did not independently carry a risk for kidney stone disease. Patients with metabolic syndrome had an OR of 1.25 for stone disease, and those with hypertension had an OR of 1.47. These studies suggest that synergistic effects of the components of the syndrome lead to an increased risk of urolithiasis. Therefore, the pathophysiology explaining increased urinary stone risk related to metabolic syndrome likely goes beyond simple cumulative effects on urine chemistry by the individual components of the syndrome. Underlying shared systemic influences are likely at play. The vascular theory of stone development is one hypothesis that attempts to link the components of the metabolic syndrome with urinary stone disease by considering a possible common systemic malfunction of inflammation and tissue damage as an underlying mechanism. However, further research is needed to investigate this hypothesis further, and to consider other possible unifying mechanisms of disease. This research will likely need to go beyond epidemiologic and urine composition studies to tease out the mechanisms behind the individual disease states themselves.

INTESTINAL CALCIUM ABSORPTION AND URINARY STONE DISEASE

The physiochemical understanding of stone formation has identified hypercalciuria as a clear risk factor for calcium-based stone formation, with increasing saturation of calcium within urine pushing crystallization and resultant stone formation. Absorption of calcium within the intestine has been associated with hypercalciuria,^{64,65} highlighting the importance of understanding the pathophysiologic mechanisms behind this aspect of calcium metabolism. A recent study by Sorensen and colleagues⁶⁶ evaluated a cohort of nearly 10,000 women followed for 20 years who were administered radioactive oral calcium assays. The impact of dietary and supplemental calcium on intestinal fractional calcium absorption and the development of urinary stone disease was determined within the cohort. Fractional calcium absorption was found to be associated with

increased risk of stone formation; however, it decreased with increased dietary calcium intake. As a result, increased intake of calcium decreased the likelihood of nephrolithiasis. The effect was noted to be a decrease of at least 45% for all levels of dietary calcium intake compared with patients in the lowest quintile of intake. This observation was thought to be from active absorption of intestinal calcium at low calcium intakes compared with passive paracellular diffusion of calcium at higher intake levels, which tends to be more linear.⁶⁷ With decreased intestinal calcium to bind to oxalate in the gut of these individuals, the oxalate is absorbed and ultimately excreted in greater concentration into the already hypercalciuric urine, increasing the likelihood for calcium oxalate stone formation.⁶⁶

This understanding of the pathogenesis of urinary stones is not only important for this disease process but also has important implications in other disease processes. For example, several epidemiologic studies have noted an increased risk of osteoporotic fractures in patients with urinary stone disease.^{68–70} This association is thought to be related to multiple risk factors, including metabolic acidosis, mutual genetic factors, and abnormal bone remodeling in hypercalciuric stone formers thought to be from elevated vitamin D levels and aberrant local cytokine and growth factor signals seen in both of these patient populations.⁶⁸ Sorensen and colleagues⁶⁶ in their study noted that women with a history of nephrolithiasis were less likely to supplement calcium in their diet, and those who did, did so at low doses. Given that low dietary calcium is associated with osteoporotic fracture risk,⁷¹ this suggests that another simple and modifiable reason for the association between urolithiasis and osteoporotic fractures is low calcium intake by stone formers. Although the influence of calcium intake on urinary stone formation is still a subject of debate, based on these data, the authors do not recommend the restriction of dietary calcium supplementation, because no clear increased risk for urinary stones has been shown. However, calcium supplementation is important for reducing the risk of osteoporotic fracture and for maintaining bone health.^{72,73}

HEAVY METALS AND URINARY STONE DISEASE

Traditionally, calcium hydroxyapatite is regarded as the predominant nidus for calcium-based urinary stone formation. A recent study has found that other heavy metal compounds may act comparably. Strontium is a heavy metal that is

processed by the human body in much the same way as calcium, as demonstrated in intestinal absorption and renal filtration studies.^{74,75} This similarly divalent cation has been observed to substitute for calcium during the process of biomineralization in bone studies, incorporating into hydroxyapatite in bones through replacing a proportion of the calcium ions.⁷⁶ These observations, and the finding that hypercalciuric stone formers were noted to have increased strontium absorption compared with normocalciuric patients,⁷⁷ have recently led to investigations regarding strontium incorporation into uroliths. Using synchrotron radiation imaging techniques on human stone samples, a recent study showed that 80% of strontium in these stones appeared as strontium apatite and 20% as strontium carbonate.⁷⁸ Although strontium research in urolithiasis is still in its infancy, this study suggests that strontium hydroxyapatite may serve as a nidus for calcium-based stone formation and could potentially serve as a valuable marker to study calcium-based stone pathogenesis.

Still elusive is a clear understanding of the initiating factors for the calcification process of urinary stone disease. For example, although Randall plaques are accepted as a nucleus for calcium oxalate stone formation,^{10–14} the process through which crystals enucleate to form the plaque remains unclear. To search for potentially responsible elements, a group in France led by Carpentier and Bazin⁷⁹ performed x-ray diffraction and fluorescence studies on human Randall plaques and kidney stones to determine their chemical compositions and the nature and amount of trace elements in each. They demonstrated that zinc levels were dramatically increased in the carboxapatite of Randall plaques compared with the carboxapatite of kidney stones. This finding suggested a role for zinc in the formation of Randall plaques in the medullar interstitium.

The Role of Calcifying Nanoparticles

Calcifying nanoparticles (CNPs), also known as *nanobacteria*, were discovered more than 25 years ago as cell culture contaminants.⁸⁰ They were originally described as novel microorganisms, and were isolated from human and bovine blood and blood products. They were characterized as fastidious and cytotoxic, and carbonate apatite-forming.⁸¹ The nature of these particles has since been debated, with contrasting theories—some describing them as a self-replicating form of life, and others describing them as a nonliving physicochemical phenomenon in the form of mineralo-protein complexes. Those who favor their

existence as nanobacteria often cite characteristics such as morphologic similarities to bacteria; presence of DNA, RNA, and bacterial proteins; and their susceptibility to antimetabolic antimicrobials. In contrast, arguments favoring their existence as mineralo-protein complexes include their extremely small size, the absence of an accurately sequenced genome, morphologic similarities to other mineralo-protein complexes, resistance to DNase and RNase activity, and proposed chemical models of formation.⁸²

Regardless of their origin, careful study has implicated these particles in the pathogenesis of multiple disease states, including polycystic kidney disease, cholelithiasis, prostatitis, HIV infection, atherosclerotic disease, and cardiovascular calcification.⁸² However, perhaps the most studied association is between these particles and urinary stone disease. Several investigators have isolated evidence of CNPs in 62% to 100% of urinary stone samples in various studies.^{81,83,84} Similarly, serum studies of patients with nephrolithiasis have also noted evidence of CNPs, with Chen and colleagues⁸⁵ evaluating a 27-patient cohort and showing CNPs in the serum of 92% of patients with nephrolithiasis, compared with 0% of controls. The mechanism through which CNPs influence urinary stone disease has been suggested to be related to an etiologic role they may play in Randall plaques. This theory was supported by Ciftcioglu and colleagues,⁸¹ who detected CNPs in more than 70% of kidney papillae samples with Randall plaques, while conversely noting that more than 80% of papillae samples without Randall plaques were free of CNPs.

Although the precise mechanisms through which CNPs may be related to urinary stone disease remain elusive, evaluation of their involvement with atherosclerotic disease and cardiovascular calcification may provide some clues. The links between CNPs and these forms of cardiovascular disease have been evaluated in multiple studies. Puskás and colleagues⁸⁶ serologically identified CNPs in most atherosclerotic plaques they examined, whereas their presence was lacking in control areas of the same vessels. Furthermore, CNPs were extracted and cultivated from most calcified sclerotic aortic and carotid samples, suggesting their involvement in atherosclerotic pathogenesis and subsequent blood vessel calcification. Similarly, Miller and colleagues⁸⁷ and Bratos-Pérez and colleagues⁸⁸ noted the presence of CNPs in calcified cardiac vessels and arterial plaques, and stenotic aortic valves, respectively. In an effort to investigate the nature of CNP arterial toxicity, Schwartz and colleagues⁸⁹ exposed a rabbit model with unilaterally damaged carotid

arteries to mineralized CNPs from kidney stones. Damaged arteries exposed to the CNPs became occluded and calcified, whereas the arteries with a healthy endothelium were resistant to exposure to the CNPs in this respect. These interesting findings note a connection between endothelial damage of blood vessels and calcification, with CNPs as a pathogenic factor. Although further studies are required to definitively establish association and theories of pathogenesis, this is one potential mechanism through which CNPs could be involved in the formation of urinary stones.

GENETIC LINKS TO URINARY STONE DISEASE

Genetic links to urolithiasis have been long established in certain heritable disorders, such as primary hyperoxaluria and the AGXT gene⁹⁰; cystinuria and the SLC3A1 and SLC7A9 genes⁹¹; and xanthinuria and the XDH gene.⁹² Familial and twin studies have suggested that calcium-based urolithiasis may also be genetically linked, with the latter studies implicating a 50% heritability for calcium nephrolithiasis.⁹³ This suspected heritability has prompted genome-wide association studies to determine candidate genes that may underlie stone formation. These studies have implicated genes encoding the calcium-sensing receptor (CASR), osteopontin (OPN), vitamin D receptor (VDR), and the claudin family of genes (particularly CLDN14) in calcium urolithiasis.^{93,94} CASR protein inhibits calcium absorption in the ascending limb in response to increased interstitial calcium. Mutations in this gene have been found to be associated with idiopathic calcium stone formation and primary hyperparathyroidism.^{93,94} Polymorphisms of the OPN gene, which encodes a urinary crystallization inhibitor, have been implicated in calcium urolithiasis.⁹³ The VDR gene has also been linked to nephrolithiasis. Polymorphisms resulting in less active versions of the gene have been hypothesized to result in increased citrate reabsorption and therefore less inhibition of stone formation.^{94,95} The CLDN14 gene was identified in a population of subjects from Iceland and The Netherlands. Polymorphisms in this gene were associated with patients showing higher urinary calcium excretion.⁹⁵

These genome-wide association studies rely on large population-based cohorts with carefully sequenced genomic data to identify subtle variations in genetic expressions. They imply that calcium-based urinary stone disease may not simply be affected by a few major genes, but rather that many genetic polymorphisms may have a sum effect resulting in increased individual susceptibility to stone formation.⁹³ The identification of

a limited set of common genetic defects that contribute to a large proportion of stone disease remains elusive, most likely because of the contributions of diet, obesity, and other environmental factors in the pathogenesis of urinary stone disease. The search for genetic links to urolithiasis is currently in its infancy but certainly holds great promise for future research into origins of urinary stone formation.

ANIMAL MODELS OF URINARY STONE DISEASE

Animal models have long been used to dissect complex disease processes into simpler components to allow for study and testing of scientific hypotheses. The known presence of various types of urinary stones and the complex, likely multifactorial causes of pathogenesis within stone types makes the use of appropriate models particularly important in urolithiasis research. As an era of whole genome sequencing is ushered in and more candidate genetic changes leading to the development of stone disease are identified, more animal models will surely need to be developed to better study the pathogenic mechanisms of stone disease in an in vivo fashion. A variety of animal models have historically been used in the investigation of urinary stone disease, including mice, rabbits, rats, and pigs. However, most studies in the literature to date have preferentially used rat models, likely because of the similarities between experimentally induced nephrolithiasis in rats with human kidney stones and the ease of inducing urolithiasis under experimental conditions. Rats have a nearly identical oxalate metabolism, can be induced to have calcium oxalate nephrolithiasis with hyperoxaluria, and produce kidney stones located on renal papillary surfaces with a similar organic and crystal matrix to humans. All of these characteristics make the rat a reasonable animal model for urolithiasis.^{96–99} Disadvantages of a rat model, however, include the high costs of breeding, care, and performance of gene knockout experiments. Many of these models also rely on the feeding of ethylene glycol to induce urinary stones, which may not be representative of a physiologic mechanism through which stones normally form. Some have also noted the potential existence of uncharacterized promoters or inhibitors of stone formation in rat metabolic pathways as downsides.⁹⁷

A novel model of stone disease using the common fruit fly, *Drosophila melanogaster*, was recently developed. The feasibility of this model was seeded in the observation that the *Drosophila* Malpighian tubule, as the site of solute transport

and excretion of calcium, uric acid, and phosphorus, is the functional equivalent of the human kidney convoluted tubule.¹⁰⁰ The use of a *Drosophila* model was first published by Chen and colleagues.⁹⁷ This team dissected and analyzed *Drosophila* Malpighian tubules with electron microscopy and x-ray spectroscopy after feeding the flies prolithogenic agents. The investigators subsequently confirmed the presence of deposited calcium oxalate crystals within the tubules. Furthermore, they were able to demonstrate appropriate changes in crystal deposition with antilithogenic agents, such as potassium citrate. Additional studies to support the translational utility of this model are currently underway by other research groups.

SUMMARY

The pathophysiology of the various forms of urinary stone disease is a complex topic. Epidemiologic research to identify high-risk cohorts and the study of urine and serum chemistries have been important in raising hypothesis-generating questions. However, many of the answers are still outstanding. Multiple, varied mechanisms have been proposed to explain the observations. Although this is valuable, the development and study of unifying theories to couple these proposed mechanisms remains the next great frontier of discovery. Genetic studies and the use of animal models will likely be important as the next steps are taken in understanding this intriguing disease and its diverse origins.

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Metabolic Evaluation of First-time and Recurrent Stone Formers

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KEYWORDS

- Diagnosis • Calcium oxalate • Humans • Kidney calculi/urine • Nephrolithiasis • Uric acid
- Urolithiasis

KEY POINTS

- Evaluation of stone formers should include careful attention to medications, past medical history, social history, family history, dietary evaluation, occupation, and laboratory evaluation.
- Kidney stones are associated with obesity, hypertension, and metabolic syndrome, and may be a harbinger of diabetes.
- Twenty-four-hour urine collections are most often appropriate for patients with recurrent stones or complex medical histories. They may be appropriate for some first-time stone formers, including those with comorbidities or large stones.
- Uric acid stones are usually associated with low urine pH, whereas calcium phosphate stones are most often associated with high urine pH. Very high urine pH suggests infection with urease-producing organisms.
- Young age and infrequent features, such as decreased glomerular filtration rate, proteinuria, or extremely high urine oxalate excretion, should lead to consideration of some rare genetic causes of stone disease, such as Dent disease and primary hyperoxaluria.

INTRODUCTION

Approximately 1 in 11 people in the United States will be affected by kidney stones at least once in their lifetime. The prevalence rate seems to continue to increase, as demonstrated by the National Health and Nutrition Examination Survey III cohort (1988–1994 and 2007–2010).¹ This increase in prevalence of kidney stones has also been seen globally. It may be attributable to changing dietary practices, increasing prevalence of diabetes and obesity,

migration from cooler rural settings to warmer urban settings, and even global warming. These increasing prevalence rates are also associated with an increase in the cost of kidney stone management to an estimated \$2.1 billion in 2000.^{2,3}

The high cost of kidney stones and the associated social expenditures, such as missed work, play a role in medical decision making for both patients and physicians.⁴ To decrease the cost and prevalence of kidney stones, it is important to provide patients with recommendations for

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prevention and control of kidney stone formation. Whether patients should receive a limited or a comprehensive metabolic evaluation regarding their kidney stone risk factors is a question frequently debated. With a relative lack of evidence-based guidelines for metabolic evaluation, it seems preferable to the authors to customize each patient's evaluation both to the individual patient's risk factors as well as other comorbidities. For instance, recent studies indicate that the prevalence of kidney stones is significantly associated with diabetes.⁵ Recognizing the links between metabolic syndrome and stones allows the physician to highlight a stone as a harbinger of insulin resistance. To address these comorbidities, current recommendations include a change in diet, exercise, weight loss, and a shift toward more dietary calcium, fluids, and less sodium.^{6,7} This article discusses the newest recommendations in the field for the metabolic evaluation of both first-time and recurrent kidney stone formers.

EVALUATION

The following discussion of evaluation applies both to first-time and recurrent stone formers. Much of these recommendations represent the practice of the authors and other lithologists and are not necessarily the result of high-grade evidence. Guidelines have been promulgated by the European Association of Urology⁸ and by a consensus panel of the National Institutes of Health⁹ and are not necessarily out of date.¹⁰ Guidelines are likely to be formulated by the American Urological Association in collaboration with the American Society of Nephrology in the coming year.

HISTORY

The past medical history, family history, and social history are all essential to determine risk factors for each patient after a first stone is passed. These histories are predictors of future recurrent stones and can help to draw conclusions that will aid in behavior modification and metabolic evaluation.

Past Medical History

Stones can be associated with a variety of medical conditions. Gastrointestinal (GI) abnormalities, like chronic inflammatory bowel disease or chronic diarrhea, can cause low urine volume and acid urine pH, which are risk factors for uric acid stones, and hypocitraturia or hyperoxaluria, which are risk factors for calcium oxalate stone formation.¹¹ Ileal resection caused by GI tract abnormalities is a common cause of kidney stones and can be

associated with chronic kidney disease; therefore, a comprehensive evaluation is necessary after the first stone. Other pertinent surgical history includes bariatric surgery. Patients with Roux-en-Y bypass are at risk for hyperoxaluria, metabolic bone disease, and nephrolithiasis.¹² A history of gallstone disease and high serum triglycerides is also associated with kidney stones, although the pathophysiology is uncertain.⁵ Sarcoidosis leads to hypercalciuria and hypercalcemia.

Hypertension and diabetes are often associated with metabolic syndrome, whose features include abdominal obesity and insulin resistance. Metabolic syndrome is associated with an increased risk of uric acid stone formation caused by the associated unduly acid urine caused by insulin resistance.^{12,13} These disorders might also be associated with more calcium oxalate stones because a greater body mass index is associated with greater urinary oxalate excretion.

Chronic kidney disease is probably associated with a reduction in stone risk because of the urinary concentration defects and the reduction in urine calcium excretion as the result of secondary hyperparathyroidism. However, some kidney diseases are associated with stone disease, such as polycystic kidney disease and medullary sponge kidney. Sjögren syndrome and other tubulointerstitial nephritides are associated with stones as the result of renal tubular acidosis (RTA).

A full list of current and past medications and supplements will be useful in the differential diagnosis of stone formation and will provide information about comorbidities. Certain medications can increase kidney stone recurrence risk. These medications include some protease inhibitors for human immunodeficiency virus (HIV), such as atazanavir; carbonic anhydrase inhibitors (acetazolamide, topiramate); triamterene; and felbamate an antiepileptic medication.¹⁴ Supplements that may increase patients' risk include vitamin C and calcium supplements.^{15–17} On the other hand, vitamin B6 and dietary calcium do not increase the risk for kidney stones and may help reduce the risk. Vitamin D does not seem to affect 24-hour urine calcium excretion and has not been shown to increase the risk of stones.¹⁸

Family History

A family history of kidney stones may suggest further evaluations. Twin studies demonstrate higher concordance for stones among monozygotic twin pairs compared with dizygotic twins, leading to an estimate that 56% of the stone phenotype is attributable to genetic factors.¹⁹ However, the genetic basis for this strong genetic

influence remains uncertain, and genetic testing is almost never part of a clinical evaluation. The exception is genotyping for primary hyperoxaluria and Dent disease in appropriate circumstances (see later discussion). Because these disorders have autosomal recessive inheritance, family history will be negative. Infrequently, autosomal-dominant polycystic kidney disease can be associated with stones and be diagnosed via any renal imaging study. RTA may also be familial and may be associated and present with stones.

Social History

Social history, particularly occupational history, is another important component of the evaluation. Patients with professions that do not allow frequent hydration or use of toilet facilities have a decreased urine output and are susceptible to stone formation. Some examples of these occupations include professional drivers (cargo transporters, taxicab drivers, chauffeurs) and primary school teachers. People who live in climates with elevated temperatures, where patients are prone to water depletion, may also have difficulty maintaining a dilute urine. Examples include people with patients in construction, athletics, or other outdoor professions. Knowing a patient's occupation can provide insight into recommendations that will keep the patient hydrated and urine dilute with a high volume.

Diet History

Understanding a patient's diet will allow one to understand possible risk factors for stone formation and then to prescribe dietary modifications to prevent recurrent stone formation. A diet high in salt contributes to excessive calcium excretion. Young people particularly have less control of their diets and often ingest more processed and packaged foods high in sodium content. Often people are unaware of their high sodium intake until it is revealed by 24-hour urine collections. Animal protein (not just beef as many lay people think) can cause hypercalciuria, hyperoxaluria, and hyperuricosuria—all factors increasing the risk of calcium kidney stone formation and often contributing to stones in athletes and body builders. Protein also increases net acid excretion and contributes to the low urine pH of uric acid stone formers. The Atkins diet and other high-protein diets are not recommended as weight loss regimens for patients with kidney disease (unless, perhaps, potassium citrate is prescribed).²⁰

More grapefruit juice consumption is associated with a higher risk for stones in both men and

women for unclear reasons, and beverages high in fructose are also associated with stones.^{21–23} Dietary oxalate content can be assessed by asking about the ingestion of nuts, dark greens (particularly spinach), concentrated and dried fruits, and chocolate. Low dietary calcium intake is consistently associated with more stones, perhaps because it allows more dietary oxalate to be absorbed by the intestine.^{24,25} Although vegetarians may have higher urinary oxalate excretion, they have fewer stones because they have higher urine volume and urinary citrate excretion.²⁶

The Dietary Approaches to Stop Hypertension (DASH) diet is high in fruits and vegetables, moderate in low-fat dairy, and low in animal protein.²⁷ The diet also contains sources of oxalate, such as nuts, legumes, and whole grains; but its variants include reduced intake of sodium, sweetened beverages, and red and processed meats.²⁸ A high DASH score is associated with a reduced risk of kidney stones.²⁸

PHYSICAL EXAMINATION

Although kidney stones have no specific manifestations on physical examination, a full physical examination is important in patients with renal colic for ruling out other conditions. Because of the correlation between hypertension and stone formation, blood pressure (BP) should be measured during the physical examination.²⁹ High blood pressure is a significant predictor of kidney stone morbidity.⁵ If treatment with thiazide-like drugs is contemplated, monitoring BP will be important.

LABORATORY EVALUATION

The most crucial component of a patient's evaluation is the laboratory evaluation of blood and urine. **Box 1** includes the relevant tests.

Blood Tests

A basic metabolic panel should be obtained for all stone formers. In addition to this routine chemistry test, measurement of serum phosphorus and uric acid may also be useful. Kidney function is assessed at baseline and over the years of the patient's history of stones. Correlations between decreases in estimated glomerular filtration rate and kidney stones have been demonstrated, although the nature of this relationship is not well established.³⁰ The decreased glomerular filtration rate associated with stones could be caused by the stone disease itself, for instance, caused by nephrocalcinosis; to recurrent episodes of ureteral obstruction; or to repeated urologic interventions.

Box 1
Laboratory evaluation of nephrolithiasis
Stone composition by x-ray crystallography or infrared spectroscopy
<i>Serum chemistry</i>
Calcium
Glucose
Sodium
Potassium
Chloride
Bicarbonate
Blood urea nitrogen
Creatinine
Phosphorus
Uric acid
Intact parathyroid hormone (if high normal to high serum calcium)
25-hydroxy-vitamin D (if low urine calcium or serum calcium)
<i>Urinalysis</i>
pH
Specific gravity
Protein
Microscopic
<i>24-hour urine</i>
For patients with recurrent stones
Some first-time stone formers

As glomerular filtration declines, risk may also decrease. Electrolytes are evaluated because hypokalemia and hypobicarbonatemia are features of RTA. Therapy with thiazides and potassium citrate will also require periodic monitoring of electrolytes.

If serum calcium levels are borderline or elevated (greater than 10.0 mg/dL, especially if hypercalcemia is present), measurement of the intact parathyroid hormone (PTHrP) level is recommended to rule out primary hyperparathyroidism as a contributing cause for stone formation. Hypophosphatemia may also be present. Primary hyperparathyroidism may be present if both serum calcium and PTHrP are at the high ends of their normal ranges, in which case ionized calcium may help confirm the diagnosis.³¹ However, secondary hyperparathyroidism should be suspected if PTHrP is high and serum calcium is at the low end of the normal range. This situation should be suspected if urine calcium is low or bone mineral density (BMD) decreased, in

which case the measurement of 25-hydroxy-vitamin D may be indicated.

A uric acid measurement may be useful in managing associated gout; when prescribing xanthine dehydrogenase inhibitors, allopurinol or febuxostat; and in monitoring therapy with thiazides.^{32,33}

Hypophosphatemia may suggest not only hyperparathyroidism but also phosphaturia related to mutations in proximal tubular phosphate reabsorption.³⁴ A measure of glucose and hemoglobin A1c can sometimes detect previously unrecognized diabetes, another risk factor for stone formation, which has health implications far beyond those of nephrolithiasis.³⁵

Urine Tests

Urinary tests for all stone formers should begin with urinalysis. The specific gravity, urine pH, and presence of protein, blood cells, or bacteria will aid in the differential diagnosis of the causes of kidney disease and renal colic. A urine sediment may reveal crystals and may lead to the recognition of drug-induced crystalluria.¹⁴ Uric acid crystals are seen in acidic urine, usually 5.5 or less, and calcium phosphate crystals in more alkaline urine, usually 6.5 to 7.0; identification can be aided if crystals are dissolved or precipitated by manipulating the urine pH *ex vivo*. Besides infection with urease-producing organisms, higher urine pH may be associated with distal RTA. Hexagonal crystals are pathognomonic for cystinuria. Struvite crystals are associated with organisms, such as *Proteus*, which produce urease and lead to high urine pH (7–9) and are a rectangular coffin-lid shape. Calcium oxalate dihydrate crystals are a tetrahedral envelope shape, whereas the monohydrate is often described as dumbbells. Urine culture should also be obtained to test for bacteria, pyuria, and infection.

Twenty-four-Hour Urine Collections

The difference in the evaluation of first-time versus recurrent stone formers has long centered on the appropriate application of 24-hour urine collections. Some reviews and consensus statements have suggested that the tests are appropriate and cost-effective only for recurrent stone formers.^{9,36} The authors do not disagree with this recommendation. It is true that the frequency of recurrence and metabolic activity of stone formation cannot be judged in first-time stone formers who present with a solitary stone. It is also clear from the authors' clinical experience that most first-time stone formers, particularly younger people, are reluctant to adhere to recommendations regarding dietary manipulation or prescription of drugs. In such

cases, generic recommendations to increase fluid intake to 3 L/d may suffice if other comorbidities discussed earlier are absent.

However, there are other people with stones who might warrant the more thorough evaluation that includes 24-hour urine collections. Perhaps people presenting with larger stones, stones requiring a trip to the operating room, or older people with other comorbidities, such as heart disease or warfarin use, should have a more detailed evaluation. Such patients are among the ones most motivated to prevent stones and can best do so when presented with the results of their own risk assessments and corresponding prescriptions, not simply the generic advice proffered to most stone formers. The European Association of Urology prescribes 24-hour collections in complicated patients: those with multiple stones or other risk factors for recurrence.⁸

In any case, it is important to emphasize that today there remains a surprising dearth of data demonstrating that prescribing preventative regimens based on urine collections is superior to offering generic advice not specific to the individual. Despite that lack of evidence, it seems evident to the authors that 24-hour urine collections are a useful tool for understanding each patient's specific urine composition to access the risk factors for recurrence and make recommendations for prevention. Spot urine collections are not as accurate because of the daily variability of urine composition caused by dietary and other circadian variations throughout the day but may be useful when 24-hour collections are not possible.³⁷

Urine collections are usually performed on the patients' self-selected diets. The analytes measured should include calcium; oxalate; phosphate; urate; urine volume; pH; and measures revealing dietary intake of sodium, potassium and protein. Based on the results, a laboratory specializing in the assessment of stone risk can calculate supersaturation of crystal-forming phases, so that changes in multiple urinary variables can be translated into a single number correlating with the stone risk. Stone composition usually correlates with urinary supersaturation.³⁸ For patients with hypercalciuria, protocols used in the past to classify the cause of the abnormality and then treat based on the results have not been shown to lead to a superior method of stone prevention, are costly and unwieldy, and are, therefore, not recommended.

At least two 24-hour urine collections should be completed before treatment is prescribed because of the additional diagnoses that multiple collections reveal.³⁹ Additional 24-hour urine

collections should be performed 4 to 6 weeks after any prescribed intervention to judge efficacy and provide patients with feedback regarding achieved success in making modifications. Laboratories that specialize in evaluating patients with stones may perform a qualitative screen for cystine for all patients new to the laboratory.

In **Box 2**, the authors briefly explicate the results of these collections. For further discussion, the reader is referred to articles in this volume regarding corresponding dietary and pharmacologic therapy.

IMAGING

Every patient presenting with kidney stones should have, if not done previously in an emergency department, an imaging study to determine the stone burden present.⁴⁵ This counting will be useful in following stone disease and judging whether prevention regimens have been successful, in ensuring that other stones do not warrant urologic intervention, in demonstrating that hydro-nephrosis has resolved, and to rule out polycystic kidney disease or other anatomic variants. Most often, computed tomography is done during emergency department visits. Although ultrasound is less sensitive and specific for stones than computed tomography, it is less expensive and does not result in exposure to radiation; therefore, it often suffices for periodic follow-up. Plain radiography is very inexpensive and entails very-low-dose radiation and may be appropriate when a known calcium stone, large enough to appear on the film, is being followed. The authors usually repeat ultrasound or plain radiography at yearly intervals for a few years after an episode of symptomatic obstruction and continue indefinitely only if metabolic activity persists.

Medullary sponge kidney is not an uncommon cause of stones and nephrocalcinosis. However, as radiocontrast administration is now relatively infrequent in stone formers, the diagnosis is likely to be made much less often.⁴⁶ It can be suspected when family members are affected and nephrocalcinosis is demonstrated. Because the disorder has no specific therapy other than addressing urine chemistry, contrast administration to find it is not recommended.

STONE COMPOSITION

Composition of stones should always be determined by x-ray crystallography or infrared spectroscopy. Both tests are relatively inexpensive and can lead to important diagnoses, especially in detecting unusual causes of stones, such as

Box 2**Twenty-four-hour urine variables**

Variables directly affecting supersaturation of stone-forming salts

Calcium: A clear demarcation of hypercalciuria cannot be clearly drawn. Risk of stones increases with increasing urine calcium excretion, even at values less than traditionally considered hypercalciuria.⁴⁰ Variations in urine calcium often correlate with urine sodium excretion and may correlate less with dietary calcium.

Oxalate: As with calcium, risk for stones increases with increasing oxalate excretion even at levels considered normal.⁴¹ Dietary oxalate is only one determinant of urine oxalate excretion, with influences of body size, calcium intake, and colonization with *Oxalobacter formigenes*.

Volume: Low urine volume (<2 L) is often related to occupation, activities, and perceived thirst.

pH: Persistently low urine pH (<5.8) is commonly associated with uric acid stones and hypocitraturia.⁴² Higher urine pH (>6.2) is commonly associated with calcium phosphate stones and RTA.⁴³ Values greater than 8.0 may suggest infection with urease-producing organisms.

Uric acid: Hyperuricosuria may be a risk factor for calcium stones, although contributes less strongly than pH to uric acid stones, and is usually the result of increased ingestion of animal protein.

Citrate: Hypocitraturia results from increased acid load, such as that resulting from increased animal protein intake or metabolic acidosis, but may also be hereditary.⁴⁴

Dietary variables affecting relevant urine chemistries

Sodium: Increased salt intake is endemic in the Western world and often is far beyond what patients imagine they are eating. It is an important variable contributing to increased calcium excretion.

Urea, sulfate: These variables reflect animal protein intake. Urea can be used to calculate protein catabolic rate to estimate protein intake. Sulfate is a correlate of dietary acid ingestion and usually approximates urine ammonium, unless nondietary causes of metabolic acidosis, such as diarrhea, are present.

Phosphorus: Excretion of phosphorus is related to dietary animal protein as well as dairy intake. Whether reduction of phosphorus intake is specifically useful for stone prevention is not known.

cystinuria or crystallization of drugs. Prescription of citrate for stone prevention can occasionally lead to increases in urine pH and might change calcium oxalate or cystine stone formers into calcium phosphate stone formers. This phenomenon is relatively infrequent because citrate prevents calcium phosphate precipitation and lowers urine calcium, but vigilance for this transformation should be maintained.⁴³

EVALUATION OF BMD

For patients with hypercalciuria and calcium stones, measurement of BMD may be useful. The strong link between hypercalciuria, low BMD, and increased fracture rate leads to the consideration of performing dual-energy x-ray absorptiometry in such patients.^{47,48} Highlighting this relationship may be of particular significance in postmenopausal women with stones who have not had BMD assessed previously. However, this relationship is also present in men. Calculation of bone fracture risk using the FRAX® tool (www.shef.ac.uk/FRAX) may also be useful. The FRAX score incorporates both the patient's risk factors and BMD to determine the 10-year probability of

a fracture. Common risk factors that affect fracture risk are age, gender, history of fracture, alcohol use, smoking, and low body mass index. The authors find that describing these links often offers patients additional motivations to increase dairy intake or take thiazides. The latter drugs reduce urine calcium excretion and are associated with the prevention of recurrent stones as well as increased BMD and reduced fracture rates.⁴⁹ Bisphosphonates may also reduce urine calcium excretion and prevent stones, although the evidence of this effect is less clear.⁵⁰ However, the possibility of prescribing these drugs when osteoporosis is found constitutes an indication for measuring BMD in stone formers.

DETECTION OF UNUSUAL CAUSES OF STONE DISEASE

As the pathophysiology and genetics of kidney stone disease are uncovered, it has become clear that some cases of genetic nephrolithiasis are escaping detection because of a lack of familiarity of clinicians with their presentations. The Rare Kidney Stone Consortium (see www.rarekidneystones.org) has been highlighting this deficiency to improve

diagnosis of cystinuria, primary hyperoxaluria, Dent disease, claudin mutations, and adenine phosphoribosyltransferase deficiency (a cause of dihydroxyadenine stones).⁵¹ Stone composition is always important, but young age, decreased glomerular filtration rate, proteinuria, and extremes of oxaluria are among the variables that should lead to more complete evaluation.

SUMMARY

Kidney stones are preventable. To maximize the efficacy of preventative regimens, the appropriate data need to be gathered. A thorough history should be directed toward assessing the past medical history, social history, occupation, activities, family history, and diet. Stone composition is always appropriate. Laboratory evaluation requires serum chemistries and urinalysis. Twenty-four-hour urine collections are most appropriate for recurrent stone formers; but some patients who are motivated to prevent recurrence and have large or complicated stones that required urologic intervention might also be appropriate candidates for complete metabolic assessment. The links between metabolic syndrome, hypertension, and obesity and stones suggest that stones may be a harbinger of important morbidity, particularly an increased risk of diabetes.

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Pharmacologic Treatment of Kidney Stone Disease

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KEYWORDS

• Allopurinol • Citrate • Medication • Nephrolithiasis • Prevention • Thiazides • Uric acid

KEY POINTS

- Thiazide diuretics, alkali citrate, and allopurinol have been shown in randomized controlled trials to decrease recurrent calcium stone formation in patients with hypercalciuria, hypocitraturia, or hyperuricosuria, respectively.
- Thiazides and alkali citrate have been shown in randomized controlled trials to decrease recurrent stone formation in unselected stone formers.
- Urease inhibitors have been shown in randomized controlled trials to decrease struvite stone formation but side effects are common and are a major concern for these medications. Urologic surgical intervention is critical for struvite stones whenever feasible.
- There are no randomized controlled trials for uric acid stones, but alkali citrate to alkalinize urine is highly effective.
- Medical expulsive therapy has been shown in randomized controlled trials to increase spontaneous stone passage and is recommended for all ureteral stones less than 10 mm if surgical intervention is not immediately indicated.

INTRODUCTION

Nephrolithiasis is a common cause of morbidity worldwide, with lifetime prevalence reported at 5% to 10%.^{1–4} In addition, recent evidence suggests that kidney stones are becoming more common.^{5,6} In the absence of pharmacologic prophylaxis, recurrence rates are high, and may be in excess of 50% within 10 years of an initial stone event.^{7,8} In general, prevention of stone recurrence is best directed at the underlying pathophysiology of stone formation and the appropriate regimen differs based on stone composition. Among patients with calcium stones, five major urinary risk factors increase the

individual's propensity: (1) hypercalciuria, (2) hyperoxaluria, (3) hyperuricosuria, (4) hypocitraturia, and (5) low urine volume.^{9,10} In addition, hypomagnesuria has also been identified as a potential contributor to calcium stone formation, although this association is less certain.^{11,12} Stone prevention in patients with calcium stones is based on treatment of these urinary abnormalities. Uric acid stones are commonly treated by increasing urine pH to increase the solubility of uric acid in urine, whereas cystine stones are treated with alkalization and thiol-binding medications to accomplish the same goal.^{13–15} Finally, urease inhibitors and antibiotics may be used as prophylaxis against struvite or infection stones.¹⁶ This

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article reviews the data on pharmacologic treatment of stone disease, with a focus on prophylaxis against stone recurrence. One of the most effective and important therapies for stone prevention, an increase in urine volume, is not reviewed because this is a dietary, not pharmacologic intervention.¹⁷ Also review are medical expulsive therapy (MET) used to improve the spontaneous passage of ureteral stones and pharmacologic treatment of symptoms associated with ureteral stents. The goal is to review the literature with a focus on the highest level of evidence (ie, randomized controlled trials [RCT]).

CALCIUM STONES

Hypercalciuria and Thiazides

Hypercalciuria is considered an idiopathic disease, with several abnormalities of calcium balance present, including increased intestinal absorption of calcium, reduced bone mineralization, and impaired renal tubular calcium reabsorption. Primary hyperparathyroidism causes resorptive hypercalciuria. Prevention of stone recurrence in patients with idiopathic hypercalciuria is commonly accomplished with thiazide or thiazide-like diuretics, whereas resorptive hypercalciuria is best treated with parathyroid surgery.

Thiazide diuretics enhance renal calcium absorption in the proximal and distal renal tubule, and thus have been the mainstay of treatment of hypercalciuric calcium nephrolithiasis. Multiple RCTs have demonstrated the benefits of thiazide and thiazide-like diuretics in the prevention of recurrent stone disease.^{12,18–22} Interestingly, only two of these trials limited their participants to those with hypercalciuria,^{18,19} whereas the remainder enrolled calcium stone formers not selected based on urinary calcium excretion. All studies that followed patients for a minimum of 2 years demonstrated a benefit of thiazide treatment. These trials all examined patients with calcium oxalate stones or unspecified calcium stones. Although there are no RCTs that studied calcium phosphate stones per se, thiazides are often used for patients with calcium phosphate stones who also demonstrate hypercalciuria. A Cochrane database review that analyzed five studies (316 patients) using thiazides or thiazide-like diuretics noted a 60% decrease in the number of new stone recurrences in patients treated with thiazides compared with placebo.²³

Potential side-effects of thiazides and thiazide-like diuretics include hypokalemia, glucose intolerance, dyslipidemia, and hyperuricemia.²⁴ A review of the RCTs of thiazide therapy for nephrolithiasis noted that serum glucose and lipids were evaluated in two of the studies and were unchanged by

therapy, serum uric acid was increased in each of the three studies that examined it, and three of four studies that measured serum potassium noted hypokalemia. Because of this latter potential side effect, potassium supplementation should usually accompany thiazide therapy to avert hypokalemia and resultant thiazide-induced hypocitraturia.²⁴ Potassium is usually administered as the citrate salt but potassium chloride can also be effective. Amiloride or spironolactone are alternatives to reduce potassium loss, but the poorly soluble triamterene should be avoided.

For patients with idiopathic hypercalciuria, typical doses of these medications are as follows: hydrochlorothiazide, 50 mg daily or 25 mg twice daily; chlorthalidone, 25 to 50 mg daily; indapamide, 1.25 to 2.5 mg daily; amiloride, 5 mg daily; and amiloride/hydrochlorothiazide, 5/50 mg daily.²⁵ There are several common strategies to avert thiazide-induced hypokalemia, which include the addition of potassium citrate or potassium chloride (10–20 mEq orally daily to twice daily, useful in patients who also have hypocitraturia) or the use of a combination thiazide/potassium-sparing diuretic, such as amiloride/hydrochlorothiazide in patients who do not require citrate repletion. Monitoring of urine pH is also critical because elevation of the urine pH greater than 6.5 can lead to supersaturation of calcium phosphate and possible change in stone recurrence composition.

Hyperoxaluria, Magnesium, Pyridoxine, and Oxalobacter

Hyperoxaluria has often been treated with dietary rather than pharmacologic intervention. Historically, patients have been advised to restrict dietary oxalate, and some have advised a calcium-rich diet in which ingested calcium binds oxalate in the stomach and gastrointestinal tract, limiting its availability for intestinal absorption and for urinary excretion.²⁶ Two pharmacologic agents that may lower urinary oxalate are magnesium and pyridoxine. In both cases, however, the data are far less compelling than those that favor thiazides.

Magnesium, a cation, forms complexes with oxalate anions in the urine, reducing the oxalate available to bind calcium and form calcium oxalate calculi. Dietary magnesium may reduce intestinal oxalate absorption in a manner similar to dietary calcium, as described previously.²⁷ There are several noncontrolled trials in the literature evaluating magnesium oxide and magnesium hydroxide preparations that reported decreases in stone recurrence rates on these medications.^{28–30} However, the single RCT that examined magnesium hydroxide versus placebo reported no difference

between treatment and placebo arms in prevention of stone recurrence.¹² Magnesium supplementation is most often used in patients with hypomagnesuria, most of whom have bowel disease. Potential side effects of magnesium therapy include diarrhea and gastrointestinal discomfort. Although less well-studied than magnesium supplementation, calcium supplementation (calcium carbonate, calcium citrate) is another potential therapeutic target for hyperoxaluria that functions by the same mechanism, complexing with oxalate anions. Supplementation of calcium is a strategy commonly used to lower stone risk for patients with a history of Roux-en-Y gastric bypass surgery, in whom hyperoxaluria is the most common urine abnormality found on metabolic stone evaluation.³¹

The rationale for use of vitamin B₆ is that deficiencies may lead to excess urine oxalate.³² The literature is lacking in RCTs regarding this use of pyridoxine for prevention of recurrent stone disease, but uncontrolled studies have shown that vitamin B₆ may decrease urine oxalate or stone recurrence in patients with calcium oxalate stones.^{33,34} Epidemiologic studies have failed to demonstrate a benefit of vitamin B₆ supplementation in men,³⁵ but did show that in women, high daily doses of vitamin B₆ (>40 mg/day) may decrease risk of stone formation compared with those who ingest little or no vitamin B₆.³⁶ A retrospective study of pyridoxine in addition to dietary counseling in patients with hyperoxaluria noted an approximately 30% decrease in urine oxalate on follow-up 24-hour urine studies.³⁷

Another potential therapy is the bacterium *Oxalobacter formigenes*, which colonizes the intestinal tract. Studies have shown that lack of colonization of this bacterium, the sole substrate of which is oxalate, may be associated with an increased incidence of calcium oxalate stone disease.³⁸ Early evidence demonstrated that oral *Oxalobacter* formulations could decrease urine oxalate excretion.³⁹ However, a recent RCT of orally administered *Oxalobacter* in patients with primary hyperoxaluria, a rare genetic calcium oxalate stone disease characterized by abnormal hepatic oxalate synthesis, failed to show differences in urine oxalate between the oral *Oxalobacter* group and placebo.⁴⁰ This potential therapy might be more successful if targeted toward patients with enteric hyperoxaluria, related to excessive absorption in the setting of inflammatory bowel disease and other causes of short bowel syndrome.

Hypocitraturia, Alkali Citrate, and Fruit Juices

Citrate is a known endogenous inhibitor of calcium oxalate stone formation; it forms soluble

complexes with calcium and reduces urinary supersaturation of calcium oxalate.⁴¹ In some cohort studies of stone formers, the incidence of hypocitraturia is in excess of 50%.⁴² Several RCTs have been performed, each using a different alkali-citrate preparation.^{43–45} Potassium citrate⁴⁵ and potassium-magnesium citrate⁴³ were both shown to significantly decrease recurrent stone formation in patients with hypocitraturia and unselected stone formers, respectively, whereas sodium-potassium citrate⁴⁴ failed to show a benefit. Potassium citrate is commercially available in tablet, liquid, and powder forms (to be mixed with water), whereas potassium-magnesium-citrate remains an investigational drug.⁴⁶ A typical starting dose of potassium citrate is 40 to 60 mEq daily in divided doses, increasing until the desired level of citraturia is reached.⁴⁶ Many clinicians monitor serum potassium 7 to 10 days after starting or changing doses of this medication. A theoretical risk of hyperkalemia exists when using potassium-based preparations, and patients with decreased glomerular filtration rate should be monitored closely when administering this medication. In addition, some patients report gastrointestinal side effects when taking potassium citrate and it is contraindicated in patients with active peptic ulcer disease. For patients with renal insufficiency or others with increased risk of hyperkalemia, sodium citrate or sodium bicarbonate may be used to increase urine citrate; however, excess sodium is another driving force in stone formation, and sodium can lead to exacerbations of congestive heart failure, hypertension, and lower extremity edema or fluid retention.

Urine citrate may also be significantly increased by ingesting beverages that are high in citrate content. In 1996, a retrospective study reported significant increases in urine citrate seen in patients who are hypocitraturic treated with a “homemade lemonade” formula (7.5 cups of water mixed with 0.5 cup of concentrated lemon juice, sweetened to taste with artificial sweetener and consumed daily).⁴⁷ Since then, several studies have tested various beverages, including other lemonade-based preparations, orange juice, pomegranate juice, lime juices, melon juice, diet sodas, and others, with equivocal results.^{48,49} In addition, a single retrospective study noted that patients on lemonade therapy demonstrated a decreased stone recurrence rate.⁵⁰ Although the potential for beverage-based therapies remains of interest to patients who prefer nonpharmacologic interventions, lemonade-based therapies have been the most well-studied and some follow-up studies have produced similar results to the initial report.⁴⁸

Hyperuricosuria and Allopurinol

Urine uric acid is thought to promote the formation of calcium oxalate stones. Uric acid reduces the solubility of calcium, called “salting out,” and promotes the formation of calcium oxalate calculi.⁵¹ Thus, hyperuricosuric calcium oxalate nephrolithiasis has traditionally been treated with allopurinol, a xanthine oxidase inhibitor that reduces endogenous uric acid production and urinary uric acid excretion. A single RCT examined stone recurrence in patients who are hyperuricosuric treated with either allopurinol or placebo and noted that the allopurinol arm demonstrated a significant decrease in stone recurrence of more than 50%.⁵² This trial excluded patients with hypercalciuria and the effectiveness of xanthine oxidase inhibition in patients with hypercalciuria has not been established. Allopurinol is typically prescribed at a dose of 100 to 300 mg daily for treatment of hyperuricosuric calcium nephrolithiasis and is often used if dietary measures to reduce urine uric acid excretion (ie, dietary protein moderation) are not successful.⁴⁶ Rare side effects of this medication include Stevens-Johnson syndrome and elevated liver enzymes. For this reason, liver function tests should be monitored several months after initiation of allopurinol therapy.⁵³ An uncontrolled trial also demonstrated that potassium citrate is effective in decreasing stone recurrence in patients with hyperuricosuric calcium oxalate nephrolithiasis.⁵⁴

Interesting recent research in uric acid metabolism may lead to novel therapies for hyperuricosuric nephrolithiasis and uric acid nephrolithiasis (see later) in the future. Specifically, recent reports of a new xanthine oxidase inhibitor (febuxostat) and a recombinant form of the enzyme uricase (Rasburicase) have demonstrated superiority to allopurinol in lowering serum uric acid and may also be more potent at reducing the frequency of gouty attacks.^{55,56} These medications represent potential therapeutic agents for stone disease but have not been tested to date.⁵⁷

URIC ACID STONES

At urine pH less than 5.5, uric acid has poor solubility in urine and the consequence of such acid urine may be formation of uric acid calculi. Some patients, despite having “normal” 24-hour urine uric acid levels, continue to precipitate uric acid stones if they have persistent “unduly acidic” urine. If urine pH is not increased, xanthine oxidase inhibition of uricosuria may be ineffective; at high urine pH, xanthine oxidase inhibition is redundant in addressing recurrent uric acid stones.

Urinary alkalization is the main strategy in the treatment of uric acid calculi and is of much greater importance than reduction of uricosuria. There are no RCTs evaluating therapies for prevention of uric acid stones but alkalization with alkali citrate is clearly so effective that randomized trials are not necessary to establish efficacy.^{13,58} A common strategy for treating uric acid calculi is to alkalize the urine as a first-line treatment and reserve the addition of allopurinol to those patients with persistently acidic urine who do not alkalize easily, such as in the presence of bowel disease, morbid obesity, or those with hyperuricemia (eg, gout and myeloproliferative disorders). Typical starting doses include potassium citrate, 4 to 60 mEq in divided doses, or sodium bicarbonate, 1300 mg twice daily, with goal urine pH between 6.5 and 7.⁴⁶ As described previously for the treatment of hypocitraturia, sodium bicarbonate is a reasonable alternative to potassium citrate for patients with renal insufficiency or other risk for hyperkalemia. Dose titration for either medication may be done by monitoring urine pH in the physician’s office or by patients at home using nitrazine paper.

STRUVITE STONES

Infection or struvite stones are those that occur as a result of chronic infection of the genitourinary tract with urease-producing bacteria, most often *Proteus*, *Pseudomonas*, *Klebsiella*, or yeast, and form at relatively high pH (typically >7). Composition of these stones is generally calcium magnesium ammonium phosphate alone, although many struvite stones also have a component of calcium phosphate (carbonate apatite or hydroxyapatite). For these stones in particular, surgical treatment is of paramount importance because it is often quite difficult to sterilize the urine and prevent recurrence if stones colonized with bacteria remain in the kidneys.

Pharmacologic prevention studies have focused on urease inhibitors and chronic suppressive antibiotics. Several RCTs have studied the urease inhibitor acetohydroxamic acid (AHA). This medication neutralizes urease, the enzyme that is central to formation of struvite stones.^{16,59,60} Hydroxyurea, another potential urease inhibitor, has not been studied in a randomized trial. Each of these studies showed a significant benefit in terms of stone prevention on this agent. It should be stressed that these trials were done before the availability of the flexible ureteroscopes that today allow the endourologist access to all calyces. The role of these drugs is not well defined in an era in which stones can be more thoroughly

evacuated with ureteroscopy. AHA administration was associated with significant side effects, and the rate of severe side effects in these studies from patients on treatment ranged from 22% to 62%.^{16,59,60} Known potential side effects include deep vein thrombosis, pulmonary embolism, headache, and tremulousness.⁶⁰ Chronic antibiotic suppression has been suggested in these patients, and there are retrospective data, but no randomized data, to support its use.⁶¹ The regimen of AHA and antibiotic suppression is typically reserved for patients who are poor surgical candidates for whom the significant side effect profile of AHA may be an acceptable risk.

For patients with struvite calculi undergoing endourologic procedures, preoperative antibiotics are commonly used. Two prospective studies of antibiotics before percutaneous nephrolithotomy versus placebo in prevention of sepsis after percutaneous nephrolithotomy noted a significant reduction in patients treated with either ciprofloxacin or nitrofurantoin.^{62,63} In addition, it is recommended for patients undergoing percutaneous nephrolithotomy to obtain intraoperative renal pelvis and stone culture, because these are the most accurate methods to identify causative bacteria should these patients develop fevers or sepsis postoperatively.⁶⁴

CYSTINE STONES

Cystinuria is an autosomal-recessive condition in which those afflicted excrete cystine in large amounts in the urine. Cystine solubility is reported at 250 mg/L, but many homozygotes with the disease may excrete in excess of 1500 mg per 24 hours, leading to chronic recurrent stone formation. Mainstays of treatment are combination therapy with urinary alkalinization and thiol-binding medications. Because of the relatively high pKa of cystine (8.5), these medications may be more effective in combination than when used alone.²⁵

There are no RCTs comparing any treatment with placebo for the prevention of recurrent cystine nephrolithiasis. Four noncontrolled trials have demonstrated that d-penicillamine and α -mercaptopyrionylglycine (tiopronin) were effective in decreasing the number of recurrent stone events in patients who are cystinuric.^{65–68} Although often well-tolerated, infrequent side effects include the following: bone marrow suppression, proteinuria with nephropathy, hepatotoxicity, aplastic anemia, drug-induced lupus, abdominal pain, diarrhea, nausea and vomiting, and anorexia. A typical starting dose of tiopronin is 200 to 300 mg three times daily (in addition to potassium citrate or sodium bicarbonate with

goal urine pH 7.5), with close follow-up of 24-hour urine composition to monitor the efficacy of treatment. It is recommended to check liver function tests, complete blood counts, and urine protein/creatinine ratios at least twice a year in patients taking these drugs. A single study that compared the two medications suggested that side effects may be less frequent for tiopronin than for d-penicillamine.²⁵

Captopril, a commonly used antihypertensive that contains a thiol-group, is another theoretical pharmacologic target for cystinuria. However, it does not appear in the urine in sufficient quantities to affect cysteine solubility and several small studies have yielded equivocal data on its ability to decrease urinary cystine levels.²⁵

MEDICAL EXPULSIVE THERAPY

MET refers to the use of pharmacotherapy to facilitate the spontaneous passage of ureteral stones. MET is based on the principal of ureteral relaxation and the increase of hydrostatic pressure proximal to the stone.⁶⁹ Clinically, the data are most compelling for the use of α -adrenergic antagonists and calcium channel blockers. Since the original description, multiple studies have revealed the efficacy of MET in increasing stone passage rate and decreasing time to passage of stones. In 2006, a meta-analysis of RCTs reported on pooled data from nine trials (N = 693).⁷⁰ The main outcome was the proportion of patients who passed stones. The authors concluded that patients given calcium-channel blockers or α -blockers had a 65% greater likelihood of stone passage than those not given these treatments. Additionally, the addition of steroids to the various regimens led to a minor benefit. After this report, other studies demonstrated the efficacy of MET for ureteral stones.^{71,72} Overall, efficacy comparing different α -blockers (tamsulosin, doxazosin, terazosin) or α -blockers with a calcium channel blocker (nifedipine) could not be determined. In another large review by Singh and colleagues,⁷¹ MET was established as a cost-effective and well-tolerated therapy. The latter was reported in a systemic review of 16 articles on medical therapy and concluded MET was safe and efficacious for moderately sized ureteral stones. A single RCT comparing alfuzosin with placebo noted that patient discomfort was significantly decreased in the treatment arm compared with placebo.⁷³

Because MET is most commonly used in the emergency department setting, Itano and colleagues⁷⁴ recently assessed the use of MET in their tertiary-care emergency department.

Of 119 patients evaluated by emergency department physicians, only 14% of patients received MET. The researchers concluded MET was under-used and recommended educational interventions in the emergency department setting. The compelling evidence for the use of MET led the American Urological Association guidelines committee to recommend that patients with ureteral stones less than 10 mm in the appropriate clinical setting (without indications for surgical intervention),

should be put on a MET regimen.⁷⁵ Major trials involving the use of MET are shown in [Table 1](#).

PHARMACOLOGIC THERAPY FOR URETERAL STENT SYMPTOMS

Ureteral stents are commonly used to promote healing and decrease obstruction and pain after treatment of ureteral or renal stones.⁷⁶ Commonly associated side effects include lower urinary tract

Table 1 Trials of medical expulsive therapy for ureteral stones					
Author/Year	Regimen	Mean Stone Size (mm)	Observation Time (d)	Mean Expulsion Time (d)	Stone Expulsion Rate (%)
1. Cha et al, ⁸² 2012	Tamsulosin, 0.4 mg	5.49 ± 1.31	28	7.82 ± 5.08	23/30 (76.6)
	Tamsulosin, 0.2 mg	5.73 ± 1.57		7.82 ± 5.08	23/30 (76.7)
	Alfuzosin	5.81 ± 1.26		8.22 ± 5.96	27/36 (75)
	Trospium	5.59 ± 1.44		13.56 ± 6.49	16/34 (47.1)
2. Al-Ansari et al, ⁸³ 2010	Tamsulosin	NA	28	6.4 ± 2.77	41/50 (82)
	Placebo			9.87 ± 5.4	28/46 (61)
3. Griwan et al, ⁸⁴ 2010	Tamsulosin	6.70 ± 1.60	28		27/30 (90)
	watchful waiting	6.33 ± 1.47			21/30 (70)
4. Pedro et al, ⁷³ 2008	Alfuzosin	3.83 ± 0.95	28	5.19 ± 4.82	(73.5)
	Control	4.08 ± 0.17		8.54 ± 6.99	(77.1)
5. Vincendeau et al, ⁸⁵ 2010	Tamsulosin	2.9	42		47/61 (77)
	Placebo	3.2			43/61 (70.5)
6. Ahmed and Al-Sayed, ⁸⁶ 2010	Tamsulosin	4.97 ± 2.24	30	7.52 ± 7.06	25/29 (86.2)
	Alfuzosin	5.47 ± 2.13		8.26 ± 7.34	23/30 (76.6)
	Placebo	5.39 ± 1.8		13.90 ± 6.99	14/28 (50)
7. Agrawal et al, ⁸⁷ 2009	Tamsulosin	6.17	28	12.3	28/34 (82.3)
	Alfuzosin	6.70		14.5	24/34 (70.5)
	Placebo	6.35		24.5	12/34 (35.2)
8. Wang et al, ⁸⁸ 2008	Tamsulosin	6.5	28	6.3	26/32 (81)
	Terazosin	6.5		6.3	25/32 (78)
	Control	6.5		10.1	17/31 (55)
9. Gurbuz et al, ⁸⁹ 2011	Hyoscine <i>N</i> -butyl bromide	6.13	14	10.55 ± 6.21	11%
	Alfuzosin	5.83		7.38 ± 5.55	52.9%
	Doxazosin	5.59		7.85 ± 5.11	62%
	Terazosin	5.48		7.45 ± 5.32	46%
10. Resorlu et al, ⁹⁰ 2011	Doxazosin males	6.5	21		29/40 (72.5)
	Doxazosin female	7.5			28/40 (70)
11. Porphiglia et al, ⁹¹ 2000	Nifedipine + Deflazacort	5.8	28	7	38/48 (79)
	watchful waiting	5.5		20	17/48 (35)
12. Cooper et al, ⁹² 2000	Nifedipine	3.9	48	12.6	31/35 (89)
	Control	3.9		11.2	19/35 (54)
13. Dellabella et al, ⁹³ 2005	Phloroglucinol		28	6.2	45/70 (64.3)
	Tamsulosin			7.2	68/70 (97.1)
	Nifedipine			6.2	54/70 (77.1)
14. Dellabella et al, ⁹⁴ 2005	Tamsulosin + steroid	6.9	28	3	29/30 (96.7)
	Tamsulosin + no steroids	6.4		5	27/30 (90)

symptoms, such as urinary frequency and urgency, pain, and decreased quality of life. Multiple pharmacologic agents have been studied whose purpose is to reduce stent-related symptoms. The most common class of medications is α -blockers.^{77,78} Two recent meta-analyses noted that the α -blockers tamsulosin and alfuzosin are each associated with significant decreases in stent-related lower urinary tract symptoms and pain and significant improvements in general health.^{77,78} The larger of these two studies examined RCTs that included 946 patients.⁷⁸

Two RCTs have also reported significant benefits from anticholinergic medications (extended release tolterodine⁷⁹ and solifenacin⁸⁰). A third RCT failed to show a beneficial effect of extended release oxybutnin, although the authors noted that their sample size was small.⁸¹

A single study placebo-controlled study examining the use of α -blockers and anticholinergic medications alone or in combination noted that combination therapy (tamsulosin with solifenacin) was associated with the greatest reduction in stent-related symptoms.⁸⁰

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Diet and Alternative Therapies in the Management of Stone Disease

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KEYWORDS

• Urolithiasis • Diet • Nutrition • Prevention • Therapy

KEY POINTS

- Nutrition therapy, widely used for secondary prevention of urolithiasis, is the application of nutritional assessment, diagnosis, intervention, and counseling to prevent or manage disease.
- Nutrition therapy for prevention of kidney stone recurrence is based primarily on the idea that the reduction of known lithogenic risk factors reduces or prevents calculus formation and growth.
- After assessment of the nutritional intake of the patient, urinary and other risk factors are evaluated with respect to their cause and whether or not nutrition intervention is likely to address them.

INTRODUCTION

Therapeutic nutrition recommendations for the secondary prevention of urolithiasis are widely used. General nutrition guidelines are useful in promoting public health and for developing nutrition plans that reduce the risk for or attenuate the effects of diseases that are affected by nutrition. Examples of such guidelines are the dietary reference intake values¹ (which include the recommended dietary allowance (RDA), adequate intake, and the tolerable upper intake level for individual nutrients) and the dietary guidelines for Americans.² However, general guidelines are insufficient in developing interventions to address specific disease conditions in individual patients. Nutrition therapy is the application of nutritional assessment, diagnosis, intervention, and counseling to prevent or manage disease.³

Food and nutrition are inherently complex. Plants grow in different soils and conditions throughout the world and therefore have variations with respect to their nutrient and molecular profiles. Animalia

of all types eat different foods and are subject to different management techniques, rendering their nutrient profiles variable. People from different cultures and backgrounds may derive the same essential nutrients but from vastly different foods and preparation methods. Conversely, the intake of certain nutrients and biologically active nonnutrients is also known to vary between cultures, between individuals, and even within individuals over time. The intake of individual nutrients or food components rarely, if ever, occurs in isolation; a single food item may contain hundreds of biologically active compounds. In the context of an entire meal, thousands of nutrients and nonnutrients are consumed. Certain micronutrients and other food constituents interact in antagonistic, synergistic, or benign ways. Individuals vary with respect to their consumption, digestion, and absorption of foods and their components, even within an individual over the course of the life span. Moreover, a single food-derived compound may affect hundreds of molecular systems and even cause epigenomic changes.⁴

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General nutritional influences on stone disease are difficult to characterize. Although interest for nutrition interventions is high among patients, evidence-based data from well-designed research studies to support specific recommendations are lacking. A recent systematic review of published randomized trials on nutritional prevention of urolithiasis collectively identified 8 trials with reasonable but variable quality, all but one reporting reduced stone recurrence (Table 1).¹³ Few studies have been designed to assess the effects of a whole diet intervention or of multiple, simultaneous nutrition interventions. Many more studies have evaluated the effects of single nutrients or individual food components, but most of these have assessed effects on stone risk factors, not stone formation. The use of stone risk factors as outcomes is attractive because it is accomplished in a shorter time frame than assessment of stone formation and growth and may be evaluated with a single diagnostic test, such as a 24-hour urine analysis. Although risk reduction alone has not been definitively tied to reduced recurrence, much of what we believe and practice about nutrition interventions to prevent recurrence comes from this assumption.

Table 1
Published randomized trials involving nutrition intervention for urolithiasis

Author, Year, Journal	Intervention	Duration
Borghi et al, ⁵ 1996, J Urol	Increased fluids vs no treatment	5 y
Sarica et al, ⁶ 2006, Urol Res	Increased fluids vs no treatment	2–3 y
Di Silverio et al, ⁷ 2000, Eur Urol	Mineral vs tap water	19 mo
Shuster et al, ⁸ 1992, J Clin Epidemiol	Decreased soft drinks vs no treatment	3 y
Dussol et al, ⁹ 2008, Nephron	Increased fiber vs decreased animal protein	4 y
Hiatt et al, ¹⁰ 1996, Am J Epidemiol	Whole diet approach (vs control diet)	2 y
Borghi et al, ¹¹ 2002, N Engl J Med	Whole diet approach (vs self-select diet)	5 y
Kocvara et al, ¹² 1999, BJU Int	Whole diet approach (tailored vs empiric diet)	3 y

NUTRITION THERAPY: THE APPROACH

Nutrition therapy for prevention of kidney stone recurrence is based primarily on the idea that the reduction of known lithogenic risk factors, such as urine supersaturation and the relative urinary excretion of lithogenic promoters versus inhibitors, reduces or prevents calculus formation and growth. In concert with pharmacologic therapy, or as monotherapy, nutrition therapy seems useful. Nutrition therapy includes the assessment of a patient’s nutritional status and intake, the diagnosis of the nutritional risk factor(s), and the development and application of the nutrition intervention.³

Role of Registered Dietitian

A registered dietitian is helpful as a member of the health care team because the application of nutrition therapy requires detailed nutrition knowledge and expertise in delivering individualized patient education. Education that is not tailored appropriately to the individual patient’s learning style, education background and nutrition knowledge, economic capacity, food preferences, and motivation to change is likely to be unsuccessful.¹⁴ Moreover, unless it is integrated into their individual regimen, patients with diabetes, Crohn disease, and cardiovascular disease likely have received specific nutrition recommendations for those conditions and thus may not embrace nutrition therapy for stone prevention. These scenarios may confound the true impact of nutrition intervention on the course of urolithiasis and might lead to the false conclusion that “dietary changes don’t work” or that “patients won’t comply.”

Empiric Versus Tailored

There are 2 approaches for applying nutrition therapy. The first is an empiric approach, applied to all patients. This approach might involve a general discussion of various nutritional strategies that address multiple risk factors and could be provided to a patient without knowing their specific urinary risk factors. If the stone composition of the patient is known, this approach could be modified by developing multiple versions of a stone prevention diet based on the patient’s previous stone composition. The second is a tailored approach that is continually monitored and altered as needed based on the disappearance or emergence of a patient’s specific risk factors. Both approaches could be termed whole diet approaches because both include recommendations about multiple foods and nutrients. One study that compared the empiric versus tailored

nutrition therapy approach reported reduced stone recurrence with the latter.¹¹ Two other studies in calcium stone formers found reduced stone recurrence with an empiric whole diet approach, but this was not directly compared with a tailored approach.^{10,12}

In practice, because of time constraints or for simplicity, urologists and other urology providers may rely more on empiric approaches such as general handouts or standardized patient instructions. Shortcomings of this approach include:

- It potentially addresses risk factors that the patient does not show, and thus may impose unnecessary recommendations.
- It does not prioritize the recommendations, which could lead to patients' confusion about what is most important for them.
- Patient compliance with nutrition and other therapies may hinge on the number of recommendations provided, with greater compliance more achievable with a short list of modifications.
- Unless otherwise addressed, it may conflict with other nutrition information that the patient has received for a different comorbidity.
- Unless otherwise addressed, specific strategies to aid the patient in achieving the

stated goals are lacking. These include, for example, behavioral modifications, recommendations for alternative food choices or different food preparation methods, changes in grocery shopping habits, education on estimating portion sizes, tips for adherence when eating out, strategies and resources for economically disadvantaged patients, and motivational techniques to encourage patients' movement along the stages of change toward action.¹⁵

Attention to these potential barriers to success of the nutrition intervention is strongly encouraged if an empiric approach is used.

Clearly, a tailored nutrition therapy approach is favorable and may avoid some of the pitfalls. In this approach, nutrition therapy is targeted to the patient's individual risk factors (**Fig. 1**), which may be different than another patient's, even if they both form the same type of calculi. Risk factors that are manifest are addressed foremost, and secondary focus is given, if appropriate, to nonexistent potential risk factors. A tailored or individual approach also allows for the integration of stone prevention strategies with nutritional therapy that the patient may have received for other conditions. By focusing on the most salient risk factors rather than discussing all potential

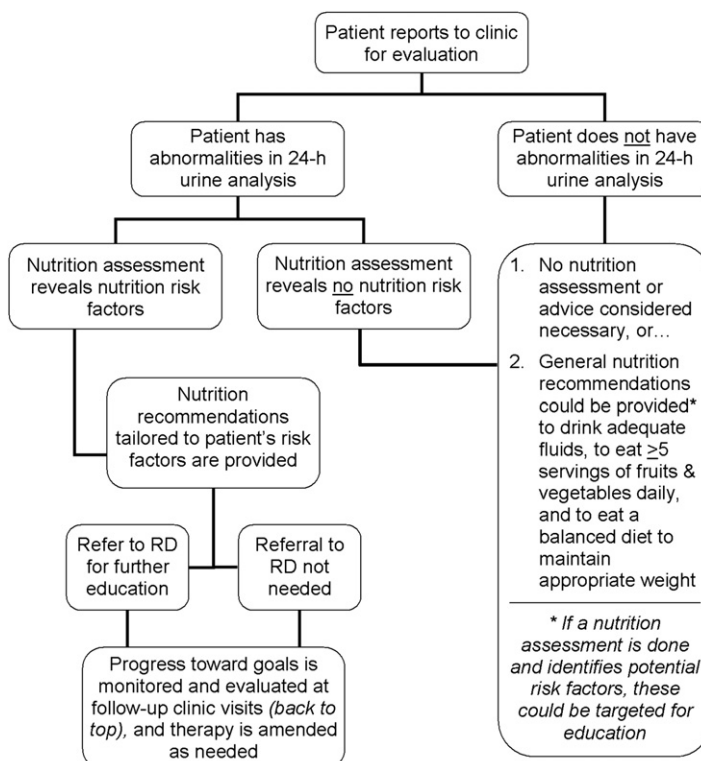


Fig. 1. Tailored nutrition therapy.

risk factors, there may be time to provide patients with pragmatic solutions to specific problems. These solutions might include how to read nutrition labels to monitor sodium intake, making appropriate food choices when eating out or during frequent travel, and titrating calcium supplementation for patients with hyperoxaluria, if needed, with a patient’s usual food calcium intake.

Lithogenic risk factors should be assessed first for nutrition influences. If nutrition is determined to be contributory, then identifying the nutrition risk is necessary in order to apply the appropriate nutrition therapy. Some risk factors have an obvious cause and solution. Low urine output, for example, is usually safely assumed as originating from a fluid intake too low to produce the target urine volume. Although it may mean compensating for extraordinary dermal, fecal, or other losses, the cause and solution remain the same, the solution being to drink more fluids. Examples of conditions without obvious cause include hyperoxaluria and hypercalciuria, each of which may manifest but for multiple different reasons. If a patient’s hyperoxaluria is caused primarily by a suboptimal calcium intake or one that is not timed with meals, then admonishing them to avoid spinach, rhubarb, beets, and chocolate without addressing their calcium intake is not likely to result in reduced urinary oxalate excretion. Similarly, if a patient’s hypercalciuria is believed to be caused primarily by acidosis and excessive bone resorption, then the most stringent of sodium restrictions may have little effect and may, as a side effect, reduce the palatability of the patient’s diet or their fluid intake.¹⁶

NUTRITION THERAPY: ASSESSMENT OF RISK

The cause of urolithiasis is multifactorial; nutritional factors are not always relevant. Risk factors associated with urolithiasis include nutritional, physiologic, medical, genetic, pharmacologic, and nonnutritional environmental. These risk factors may exist singly or in concert with one another. Nutritional factors and specific physiologic and medical conditions with nutritional implications are addressed later, after which follows a description of the nutritional implications of commonly assessed urinary risk factors. Calcium and uric acid stones are addressed, although aspects of the specific nutrition therapies presented may apply to patients who form cystine, struvite, or other stones.

Nutritional Risks in the Diet

Assessment of a patient’s habitual diet and use of over-the-counter supplements is useful in

determining where there may be excesses, deficiencies, or imbalances of nutrients and other food constituents that are not nutrients but that are relevant to kidney stones. Techniques used by a registered dietitian could include a 24-hour diet recall conducted one-on-one with the patient (either with or without the use of nutrient analysis software), a multiple-day diet record kept by the patient and returned to the dietitian for analysis, or a targeted assessment that evaluates the most relevant nutritional factors. In the nutrition assessment, the dietitian considers a combination of general age-specific and gender-specific nutrition guidelines as well as accepted therapeutic nutritional recommendations for certain medical conditions¹⁷ (see next section). The nutrition diagnosis should focus on the nutrition-related cause for or contributor to the patient’s risk for urolithiasis. In the case of hyperoxaluria, an example of the nutrition diagnosis is “Increased nutritional lithogenic risk related to suboptimal calcium intake not timed with meals, contributing to low oxalate binding potential in gastrointestinal tract and resulting in hyperoxaluria.”

The following may be considered the major nutritional factors that contribute to increased lithogenic risk:

• Low fluid intake	• High urine supersaturation
• Excessive sodium salt intake	• Hypercalciuria, hypocitraturia
• High intake of refined carbohydrates	• Hypercalciuria
• Excessive caffeine or alcohol intake (especially by sensitive patient subpopulations)	• Hypercalciuria, hyperuricosuria (alcohol)
• Overall diet habitually high for potential renal acid load	• Hypercalciuria, hypocitraturia, acid urine
• Excessive supplementation (exceeding physiologic needs or the RDA) of calcium	• Hypercalciuria
• Low fruit/vegetable intake	• Hypocitraturia, acid urine
• Intake of high-oxalate foods, especially with low calcium intake	• Hyperoxaluria

- | | |
|---|------------------------------|
| • Suboptimal calcium intake | • Hyperoxaluria |
| • Excessive intake of some over-the-counter supplements such as vitamin C, and possibly some herbal or plant-derived concentrates (eg, cinnamon, cranberry, turmeric) | • Hyperoxaluria |
| • Excessive calorie intake resulting in overweight | • Acid urine, hypocitraturia |

Aside from single foods or food groups, overall dietary patterns seem to be more or less risk-conferring than others.¹⁸ For example, data confirm that the Atkins diet for weight loss¹⁹ or the ketogenic diet for seizure disorders²⁰ can both increase risk for stone formation. Disordered eating patterns, by people with pica or other eating disorders, may also result in increased risk for urinary tract stones.²¹ Vegetarian diets, despite typically being higher in oxalate, are associated with reduced risk,²² as was a low-salt, adequate-calcium, moderate-protein diet (not unlike the dietary pattern known as the dietary approaches to stop hypertension [DASH] diet).¹² Recently, specific gastrointestinal microbiotic profiles have been identified, containing discrete combinations of bacterial species, and these seem to be regulated in large part by dietary patterns.²³ For example, people who consume high-fiber diets have a different microbiotic profile than those who do not.²⁴ Another study showed that people whose diets are rich in meats have a different bacterial enterotype than those whose diets are rich in carbohydrates.²⁵ As research progresses, it is possible that certain dietary patterns could result in changes in the gut microbiome that could be linked with antilithogenic effects, such as a more favorable concentration of oxalate-degrading bacteria.

Nutritional Risks Related to Specific Physiologic and Medical Factors

Diabetes confers known risks for urinary tract stones.²⁶ It is not clear whether good control of diabetes with prescribed diabetic nutrition interventions results in reduced stone risk. However, it seems intuitive that appropriate control of insulin

and blood glucose through nutrition and pharmacologic therapy would be helpful, especially with the integration of specific nutrition strategies to reduce stone risk factors. Malabsorptive conditions, including Crohn disease, celiac sprue, short bowel, postgastric bypass or duodenal switch, and chronic diarrhea, confer well-known risks for urinary tract stones.²⁷ Multiple nutritional strategies to attenuate the malabsorptive effects of these conditions may be used that could have antilithogenic effects. Although not a nutritional problem per se, chronic or frequent antibiotic use could reduce gastrointestinal bacteria capable of degrading oxalate.²⁸ Every course of antibiotics tends to deplete beneficial bacteria, and in the months required to recover these, pathogenic bacteria may grow.²⁹ Nutritional and supplemental means, such as probiotic foods and supplements and foods rich in prebiotic components, are capable of altering and optimizing gut bacterial profiles; nutrition therapy may thus play an important role in addressing urolithiasis risk in the setting of antibiotic exposure.^{23–25}

Nutritional Implications of Urinary Risk Factors

The analysis of a 24-hour urine versus a spot urine collection is necessary to account for diurnal and other rhythmical excretion patterns of various products of metabolism. Multiple analyses over time are most useful in establishing risk and in monitoring changes.³⁰ Parameters commonly measured and monitored to predict risk of lithogenesis are: calcium, oxalate, uric acid, urine pH, urine volume, phosphate, citrate, magnesium, and supersaturation indices for specific crystalloids. Where cystinuria is suspected or known, cystine is measured. Urinary phytate could be measured, because it is a potent inhibitor of calcium lithogenesis, but it is not currently assessed by major commercial laboratories.³¹

Many of the urinary parameters monitored for stone risk are related to nutritional intake but are not necessarily surrogates for intake. For example, calcium is under tight homeostatic control, and its excretion in urine is not always related to intake.³² Sulfate, although commonly used as a surrogate for meat intake, may also reflect the intake of soy beans and foods made from soy (eg, tofu, tempeh), because soy is rich in methionine. Frequently, more than 1 parameter in the 24-hour urine collection must be viewed together and, in addition to the nutrition assessment, may provide a good picture of what is going on in the diet.

Other parameters frequently measured in urine may not be risk factors for renal stone formation

per se but may (1) contribute indirectly to lithogenesis by altering renal handling of other excretory products, (2) be used for calculation of urine supersaturation, or (3) provide information to corroborate or rule out underlying disorders or nutritional contributors. These parameters include sodium, potassium, sulfate, ammonium, chloride, urine urea nitrogen, and protein catabolic rate (calculated from the product of urine urea nitrogen and a factor accounting for the average nitrogen content of dietary proteins, divided by the patient's body weight). Although this latter group of urine parameters may be useful in estimating nutritional potentiates of stone formation and growth, many may be altered in the setting of underlying disorders, and none are perfect biomarkers for intake; nutritional assessment of the patient's diet is thus imperative.

NUTRITION THERAPY: IN PRACTICE

After assessment of the nutritional intake of the patient, urinary risk factors for urolithiasis are evaluated with respect to their cause and whether or not nutrition intervention is likely to address them. Frequently, multiple risk factors are present in a patient's 24-hour urine analysis. If nutrition therapy to address multiple risk factors is applied, the need to integrate them into a whole diet,

addressing any contradictions between recommendations, is important. This strategy includes the need to integrate stone prevention strategies with nutrition strategies that the patient is following for any other health condition.

Hypercalciuria

Assess for nutrition contributors (Fig. 2). Sodium, acid load of diet, gastrointestinal and renal calcium handling, and omega-3 fatty acids are addressed.

Sodium

Sodium exerts a potent hypercalciuric influence because of expansion of extracellular volume and competition between sodium and calcium ions in the renal tubule.³³ If dietary sodium seems contributory to hypercalciuria, assess food source(s), focusing not only on notoriously high-sodium foods but also on foods that are not necessarily high in sodium but, when consumed in large quantity, confer a high sodium load (Table 2). Foods at the top of the list for sodium content include miso, table salt, canned sauerkraut and tomato sauce, cured ham, and baking soda, all of which provide more than 1000 mg sodium in a single serving.³⁴ However, these are not necessarily foods that patients might eat every day or in large quantity. On the other hand, foods that are far lower on the sodium content scale

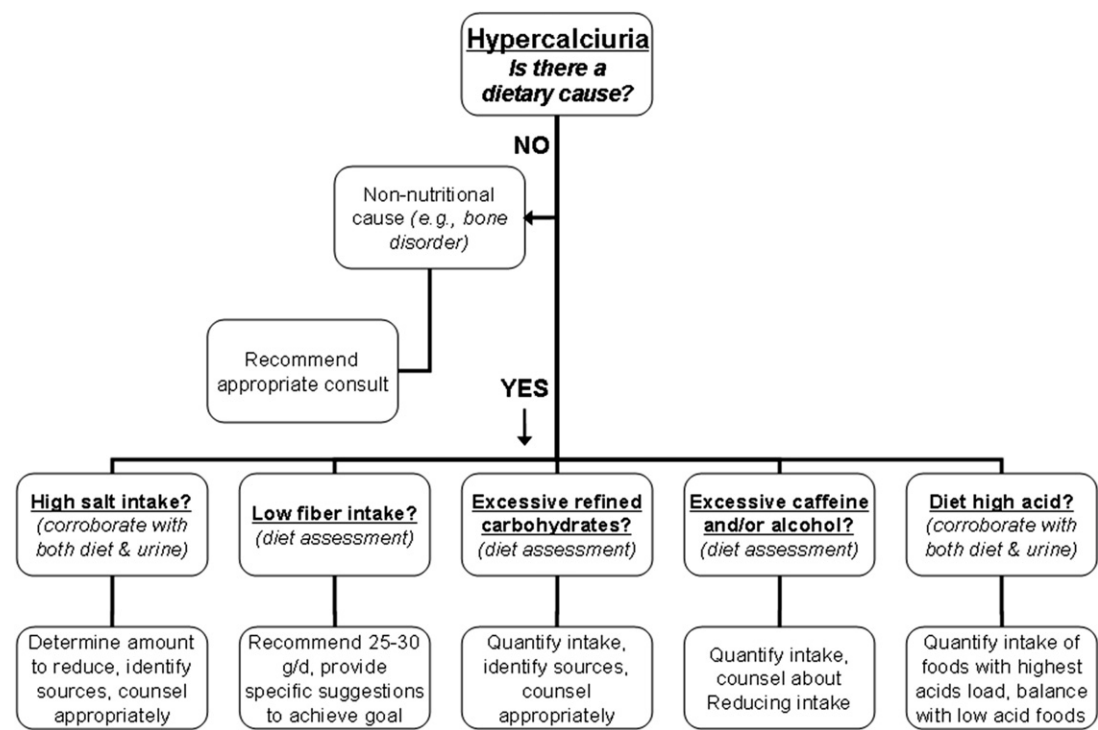


Fig. 2. Nutritional contributors to hypercalciuria.

Table 2
Nutritional sodium sources identified from multiple-day weighed-diet records of stone-forming patients at a stone clinic

Food Group	Contribution to Total Sodium Intake (%)	Cumulative Percentage Toward Total Sodium Intake
Luncheon meats and other processed meats	14	–
Breads and baked goods (bagels, buns, muffins, rolls, tortillas)	14	28
Added salt (NaCl) and spices containing salt	14	42
Canned soups/vegetables and pickled goods	9	51
Salad dressings, condiments, spreads, sauces	8	59
Salty snacks (chips, pretzels, popcorn, candy)	7	73
Homemade casseroles, soups, and other mixed dishes	7	80
Cheese and cheese products	7	66
Pizza and prepared sandwiches (including fast food)	6	86
Meal starters and helpers (eg, pasta and rice mixes)	5	91
Breakfast cereals	5	96
Milk, yogurt, frozen dairy	3	99
Miscellaneous	1	100

Data from Penniston KL, Wojciechowski KF, Nakada SY. The salt shaker provides less than 15% of total sodium intake in stone formers: food strategies to reduce sodium are needed. *J Urol* 2011;185:e861.

are sometimes items that are eaten daily in high quantity.³⁵ For example, 5 servings of bread, which is easily achievable with 2 pieces of toast in the morning, a sandwich at lunch, and a roll at dinner, could provide as much or more than 1000 mg sodium. These foods and their intake patterns must be identified when providing nutrition therapy if sodium intake is determined to be a nutritional risk factor.

Acid load of diet

Dietary acid load has a well-known effect on urinary calcium excretion, believed to be caused by reduced renal tubular calcium reabsorption, increased glomerular filtration rate, increased bone mineral mobilization to buffer the acid load, or increased intestinal calcium absorption.³⁶ To address the acid load of diet if it is a suspected contributor, intervention aims to balance the intake of high-acid foods with low-acid or alkaline foods. A scale has been developed to estimate the potential renal acid load (PRAL) of foods.³⁷ It accounts for the anion/cation ratio of a food and has been suggested as a reasonable model for estimating

the effects of the diet on renal net acid excretion. Foods conferring an acid load caused by the amount of sulfur in their amino acid structure include:

- All foods of flesh origin, including those from land and water
- Cheese, all types
- Eggs, largely from the yolk
- Grains, nearly all types, especially when consumed in high quantity

Milk, yogurt, and fats are neutral on the PRAL scale. Foods conferring an alkaline load (negative numbers on the PRAL scale) include nearly all fruits and vegetables. The few fruits and vegetables that have a slight acid load, and these include cranberries and lentils, need not be restricted, because the magnitude of their acid load is so much lower than that of the high-acid foods so as to be negligible. Moreover, fruits and vegetables are usually recommended to be increased, and the unnecessary restriction of some is a frequent source of frustration and confusion for patients.

Gastrointestinal and renal calcium handling

Reducing the gastrointestinal absorption of calcium in an effort to reduce the renal filtered load could be considered in those who are not at risk for calcium deficiency. Fiber may reduce the amount of gastrointestinal calcium absorbed.³⁸ If fiber intake is not at recommended levels (25–30 g/d for most adults), and if calcium and bone status seems normal, then it is appropriate to recommend increased fiber intake from foods or in combination with over-the-counter fiber supplements. Because of a high binding affinity, oxalate is also capable of reducing gastrointestinal calcium absorption, and its intake has been correlated inversely with urinary calcium excretion.³⁹ A high intake of carbohydrates may contribute to hypercalciuria, although it may be a transient effect.^{40,41} If nutritional assessment suggests that a high carbohydrate intake is contributory, especially of refined carbohydrates (eg, sweetened beverages and juices, candy, refined grains, and foods made from them), intake should be reduced by suggesting whole-grain alternatives, whole fruits instead of juices, and nonsweetened beverages and foods. Caffeine and alcohol may contribute to urinary calcium excretion, but the need to limit or restrict these compounds should be individually assessed based on the amount typically consumed and on patient preferences.^{42,43}

Omega-3 fatty acids

Some reports suggest efficacy of omega-3 fatty acids in reducing urinary calcium excretion,^{44–46} and these may be supplemented using commercially available, over-the-counter formulations. However, the dosages required to achieve reduced urinary calcium excretion are unclear.

Hyperoxaluria

Assess for nutrition contributors (Fig. 3). Calcium intake, food oxalate, and over-the-counter supplements are addressed.

Calcium intake

If the nutrition assessment reveals a low calcium intake, or one that is not timed with meals, there could be a lack of oxalate-binding potential in the gastrointestinal tract.⁴⁷ For most patients, it might be sufficient to recommend consuming something containing around 300 mg of calcium at each meal daily. Assuming 3 meals daily, this figure would provide 900 mg of calcium from calcium-rich foods or beverages alone. Considering that other foods in a generally balanced diet collectively provide, on average, around 300 to 400 mg calcium, there is no need to supplement in this scenario. Special strategies for calcium intake that meets both physiologic needs and enhances binding potential for oxalate must be devised for: (1) patients who are

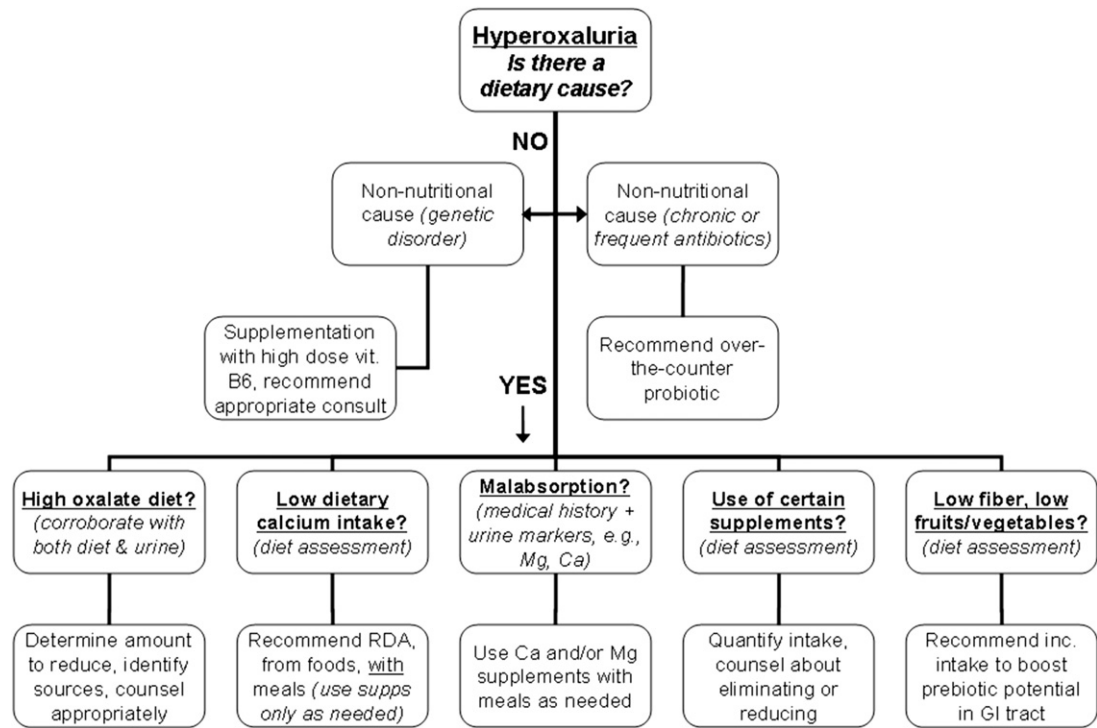


Fig. 3. Nutritional contributors to hyperoxaluria.

lactose intolerant or otherwise do not use dairy foods, which are among those highest in calcium per serving, (2) those who do not eat regular meals daily, (3) those who snack or graze frequently throughout the day instead of eating discrete meals, and (4) those who have altered gut physiology or any other condition resulting in malabsorption, because the extraordinary fecal calcium in these individuals is bound to fatty acids, resulting in less calcium available to bind to oxalate. A combination of foods and supplements, frequently large doses but always timed with meals, is usually required in these cases. Magnesium is also known to bind oxalate in the gut and thereby reduce its absorption⁴⁸ and could also be incorporated into nutrition therapy.

Food oxalate

The restriction of food-derived oxalate is controversial. For the most part, foods that contain oxalate are healthy foods and, moreover, are frequently those conferring general health benefits and specific nutrients that are often underconsumed, including fiber, potassium, magnesium, and antioxidants. Elimination or restriction of such foods may do more harm than good, especially if other strategies could be used, such as appropriate calcium (and magnesium) intake timed with meals and snacks. A reduction of dietary oxalate also requires a simultaneous reduction in dietary calcium in order to maintain an appropriately low calcium/oxalate ratio in urine, and some have questioned the value of the low-oxalate strategy for this reason.

The relative bioavailability of oxalate in foods is another topic of interest, because foods high in oxalate might not necessarily be those from which oxalate is readily absorbed.⁴⁹ Although more research is needed on the different forms of dietary oxalate, it is assumed that the less water soluble the oxalate, the lower its bioavailability. Thus, restricting high-oxalate foods based on their oxalate concentration without accounting for bioavailability could result in unnecessary restriction. Research to confirm and identify foods with high oxalate bioavailability is needed. Oxalate is a prebiotic for oxalate-degrading bacteria.⁵⁰ Although there may be no need for oxalate-degrading bacteria in the gut in a setting of a low oxalate intake, bacteria capable of degrading oxalate may also provide other biological benefits and serve as part of the microbiome required for optimum health status. (Table 3 provides definitions for and examples of food probiotics and prebiotics.)

Therefore, if dietary oxalate seems contributory to hyperoxaluria, focus not only on foods that are

known to be high in oxalate but also on foods that are not necessarily high-oxalate but, when consumed in large quantity, confer a high oxalate load (Table 4). Several of the oft-cited high-oxalate foods are not necessarily those that are consumed daily or in high amounts. Rather than focusing on the few pieces of rhubarb pie a patient might have in a year, a better strategy is to identify foods with appreciable oxalate that are eaten habitually and in high amounts. Depending on the individual, these foods might include chocolate, nuts and seeds, spinach, potatoes, and potato chips. In addition, because whole grains are frequently ample for oxalate but not necessarily identified as high in oxalate, and because grains are frequently eaten multiple times in a day, these can be a source for oxalate (see Table 4).⁵¹ Discretion in recommending reduced oxalate intake must be used and individual plans developed for patients who rely on nuts and seeds as a protein source or as a low-carbohydrate snack and for those who are vegetarian and who enjoy ample fruits, vegetables, and whole grains. Recommendations to avoid all oxalate in these situations might reduce the nutritional quality and diversity of the diet, not to mention risking diminished compliance.

Over-the-counter supplements

Over-the-counter supplements have been implicated in increased urinary oxalate excretion, and these include cinnamon, turmeric,⁵² and cranberry.⁵³ Others are associated with reduced oxalate excretion, and these include omega-3 fatty acids^{46,54} and pyridoxine (vitamin B₆).⁴⁴ The dosages required to achieve reduced urinary oxalate excretion with omega-3 fatty acids are unclear and its success in practice is not well characterized. Similarly, although supraphysiologic supplementation with pyridoxine is used in patients with primary hyperoxaluria to address enzyme deficiencies, its effectiveness and practice in patients with idiopathic or enteric hyperoxaluria are not well characterized.

Hyperuricosuria

Assess for nutrition contributors. Purine intake, alcohol and fructose, and acid load of diet are addressed.

Purine intake

Some foods that are rich in nucleoproteins known as purines may contribute to hyperuricosuria, because uric acid is an end-product of purine metabolism.⁵⁵ The average daily intake of purines seems to range between 500 and 1500 mg.⁵⁶ Virtually all foods have some purines, but those

Table 3
Definitions for and examples of probiotics and prebiotics

Definition	Mechanism	Examples	Food Sources
Probiotics			
Live, nonpathogenic microorganisms in the gastrointestinal tract that confer a health benefit on the host when administered in adequate amounts	Effects are strain specific (not species or genus specific) and include immune modulation, production of antimicrobial compounds, and maintenance of gut integrity and function	Certain variants of: Lactobacilli Bifidobacteria Streptococci Bacilli Yeasts	Cultured yogurts and fermented dairy products, aged cheeses, some nondairy products (eg, soy milk), fermented foods, over-the-counter supplements, chewing gum, lozenges, infant formulas
Prebiotics			
Nondigestible food component or ingredient that beneficially affects the host through effects on the microbiome	Must reach the large intestine intact, where overall effect is to selectively stimulate growth or activity of 1 or a limited number of bacteria or to directly stimulate immunity, protect against pathogens, and facilitate host metabolism and mineral absorption	Certain nondigestible carbohydrates, including: Inulin Various oligosaccharides Pyrodextrins Fructan Lactulose Lactitol	Fruits (especially bananas, berries, kiwi), vegetables (especially onions, garlic, leeks, artichokes), whole grains (especially oats, barley), and whole-grain foods, honey, over-the-counter supplements, powders, commercial extraction of chicory root, fortified foods

Data from Saulnier DM, Spinler JK, Gibson GR, et al. Mechanisms of probiosis and prebiosis: considerations for enhanced functional foods. *Curr Opin Biotechnol* 2009;20:135–41; and Figueroa-Gonzalez I, Quijano G, Ramirez G, et al. Probiotics and prebiotics–perspectives and challenges. *J Sci Food Agric* 2011;91:1341–8.

most concentrated (providing up to 1000 mg per serving of 85–113 g [3–4 ounces]) include anchovies, sardines, organ meats (eg, brain, liver, kidney), and glandular tissue, commonly referred to as sweetbreads. Appreciable amounts of purines, up to 100 mg per serving of 85 g to 113 g (3–4 ounces), are provided by shellfish, game meats, water fowl, mutton, beef, pork, poultry, and fish.⁵⁷ As with other nutrition recommendations, the patient who does not typically eat purine-rich foods does not benefit from advice to limit or eliminate them from their diet. If nutrition assessment documents a high intake of purine-rich foods, education about lowering dietary purines is appropriate. Avoiding the foods highest in purine concentration and reducing recurrent intake of those with lower concentrations would be recommended. Foods of plant and dairy origins contain purines, but the impact of these on uric acid synthesis is different. A recent study in men with gout concluded that vegetable-derived

purines did not increase risk and dairy foods lowered risk.⁵⁸ Thus, patients are unlikely to benefit from avoiding plant and dairy foods that contain purines because they might compromise their vegetable intake, calcium intake, and the diversity of their overall diet.

Another potential concern is the tendency to refer only to red meat as the major culprit with respect to uric acid synthesis. Recently, fish and chicken were reported to increase both serum and urine uric acid to the same degree as or higher than red meat.⁵⁹ Recommending reduced red meat intake may cause the patient with hyperuricosuria to substitute with more chicken and fish, when a reduction of all of these foods may be necessary to achieve favorable results. The amount of reduction should be individually titrated based on the current amount of these foods the patient eats. Reduction could occur with reduced portion sizes, reduced frequency of intake throughout the week, or both. Patients usually

Table 4
Nutritional oxalate sources identified from multiple-day weighed-diet records of stone-forming patients at a stone clinic

Food Group	Contribution to Total Oxalate Intake (%)	Cumulative Percentage Toward Total Oxalate Intake
Nuts, seeds, nut butters	26	–
Spinach	12	38
Breads, flours, baked goods	12	50
Cereals	7	57
Potatoes (includes sweet potatoes), French fries	7	64
Leafy vegetables, nonspinach	6	70
Mixed dishes, casseroles, meats	6	76
Nonleafy vegetables	5	81
Chips, crackers	5	86
Chocolate	5	91
Soymilk, kefir, cheese	4	95
Tea, spices	2	97
Fruit	2	99
Pasta, rice	1	100

Data from Penniston KL, Wojciechowski KF, Nakada SY. Dietary oxalate: what's important and what isn't for patients with calcium oxalate stones? J Urol 2011;185:e824–5.

require assistance conceiving of alternate means for obtaining protein, especially if their protein intake is compromised by compliance with the recommendation.

Alcohol and fructose

Alcohol is a contributor to uric acid biosynthesis, because it enhances purine degradation and increases xanthine oxidase expression, which is the enzyme that catalyzes the final step in uric acid production.⁶⁰ Fructose, a monosaccharide found naturally in sucrose (table sugar) and fruits and also used ubiquitously in food manufacture and production as a sweetener, has also been suggested to increase serum uric acid and potentially urinary uric acid excretion.^{61,62} The nutrition assessment should quantify the intake of both alcohol and fructose in the patient with hyperuricosuria and discuss ways to reduce intake if it is believed to be contributing to stone risk.

Acid load of diet

Although not a contributor to uric acid biosynthesis and the urinary excretion of uric acid, the acid load of the diet can reduce urine pH such that urinary uric acid is less soluble. Refer to elsewhere in the text for addressing and correcting acid load of diet if the nutrition assessment identifies it as a risk factor.

Hypocitraturia

Assess for nutrition contributors (**Fig. 4**). The acid load of the diet, dietary citrate, chronic or frequent diarrhea, and sodium are addressed.

Acid load of diet

If the diet is assessed as high for acid load, which exerts a hypocitraturic effect because of enhanced renal citrate reabsorption,⁶³ reducing the acid load with smaller amounts of cheese, meats, and other flesh foods would be advised.³⁷ Specific strategies to achieve this goal could be tailored to patients' needs. For example, for the patient unable or unwilling to give up meat or some other flesh food at both lunch and dinner, a specific recommendation for smaller portions at each of these meals could have the same effect as eating those foods at only 1 meal of the day. If a patient's calorie load is not a concern, simply balancing their present intake of high-acid foods with an appropriate quantity of low-acid or alkaline foods (ie, most fruits and vegetables) could be suggested.

Dietary citrate

Although citric acid does not fit the definition for a nutrient and thus does not have a recommended intake or RDA, increased intake from foods and beverages may enhance urinary citrate excretion.^{64–67} This goal could be achieved with specific

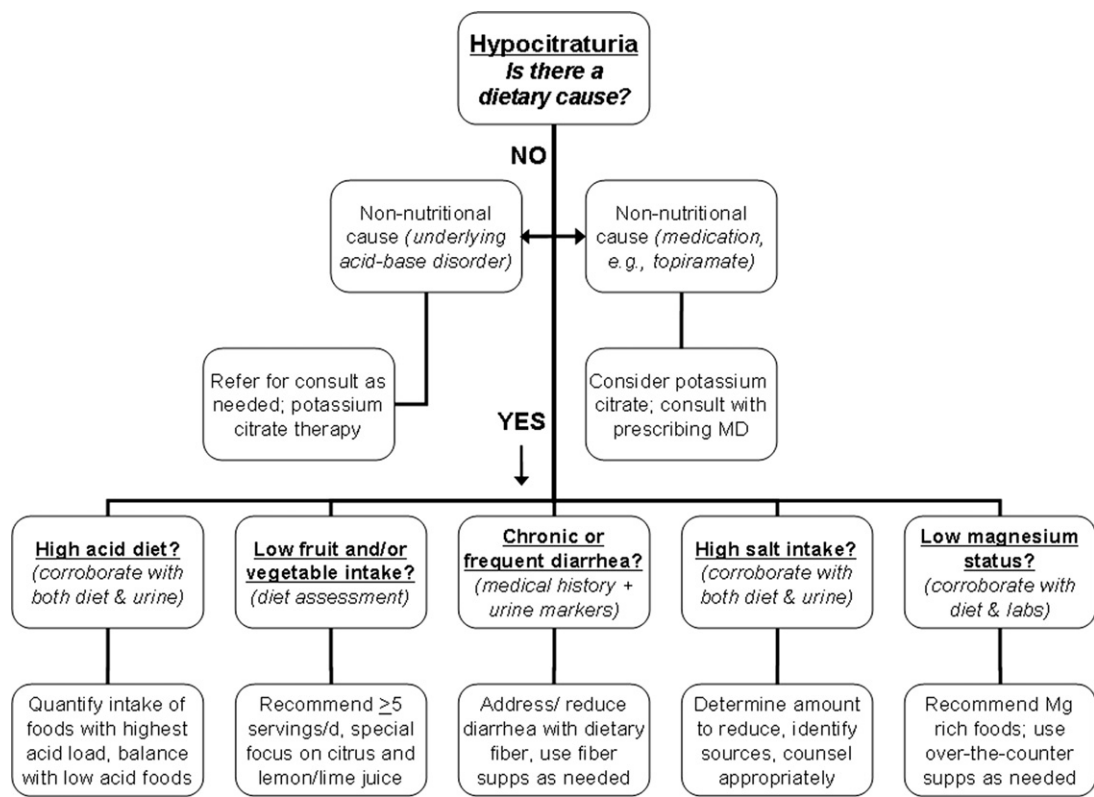


Fig. 4. Nutritional contributors to hypocitraturia.

recommendations about using lemon or lime juice, which are particularly concentrated with citric acid, diluted in water or another beverage to prevent degeneration of tooth enamel. Recommendations to use commercially available, ready-to-consume lemonade preparations, especially if they are not sugar-free, are rarely if ever indicated, because they contain a minimal amount of lemon juice and provide ample carbohydrates and food calories. Recommendations for increased citrus fruit intake might be incorporated and would provide beneficial nutrients as well, such as fiber, potassium, antioxidants, and prebiotics.

Recently, low-sugar, low-calorie beverage drinks flavored with citrate and other organic acids were suggested as agents capable of enhancing urinary citrate.⁶⁸ Depending on the urinary citrate level targeted as therapeutic for an individual patient, specific volumes of these beverages could be recommended and may also have a side benefit of increasing overall fluid intake. However, the ability of diet-derived citrate to fully correct severe hypocitraturia is questionable, but this may depend on the magnitude of the patient's hypocitraturia and on other nutritional and physiologic factors.

Chronic or frequent diarrhea

If frequent diarrhea is believed to be contributory to hypocitraturia, because of excessive bicarbonate losses in stool resulting in enhanced renal citrate reabsorption, nutrition strategies to correct diarrhea can be used.⁶⁹ Increased dietary fiber, with a specific focus on insoluble versus soluble as determined by the specific situation, could be recommended and specific strategies provided to achieve the goal. Over-the-counter fiber supplements, of which there are multiple varieties, may be beneficial in addressing and stemming diarrhea, and this could result in correction of hypocitraturia.⁷⁰ A growing body of literature supports probiotic supplementation for correcting diarrhea, and multiple probiotic formulations are commercially available and could be tried.^{71,72}

Sodium

If a high sodium salt intake is considered contributory to hypocitraturia, refer to the section on sodium under hypercalciuria earlier in the text.⁷³

Low Fluid Intake

Fluids of any kind help promote urine output and may be the single most useful way to reduce

recurrence risk.⁵ Low-sugar, low-calorie beverages are most desired, but it is acceptable to count other beverages toward one's fluid intake; a diversity of different fluids, most of which are noncaloric, should be encouraged.

Fluid intake may be considered low when urine output does not meet the target volume. It may help to explain to a patient that they may require more fluids than another patient to produce a target amount of urine given variable extrarenal fluid losses between individuals depending on such factors as how much a person sweats or how much they lose in stool. It may also be helpful to identify the day of the week that the person carried out the 24-hour urine collection on which the assessment of low urine volume is made. Some people have ample fluid intakes during the workweek, when they are eating and drinking in more or less a similar pattern, and may even be conscious of drinking a certain volume of fluids, but on a weekend or nonwork day, schedules and dietary patterns are frequently different. Knowledge of how a patient drinks throughout the week, accounting for workday versus non-workday differences, helps to address specific days when fluid intake is suboptimal.

Some patients benefit from more specific advice than to simply increase fluid intake. In these situations, a fluid intake schedule can be devised. By breaking the day into 3 equal sections (eg, of 5 hours each depending on the patient's lifestyle), with advice to drink about 1200 mL of fluids in each section, a person could consume approximately 4 L (120 ounces) of fluids. It may be helpful to ask the patient to use a fluid container with visible volume measurements to make meeting the specific goal easier. Carrying a fluid container was identified as an important cue to action in a recent analysis of factors influencing fluid intake in stone formers.⁷⁴ As necessary, fluid recommendations should compensate for excessive dermal or fecal losses, and patients may need to be educated as appropriate to their lifestyle and comorbid conditions.

Those at particular risk for low fluid intake for other reasons may require special attention. These at-risk groups include those with occupations requiring self-censorship of fluid intake because of lack of access for long periods to restrooms⁷⁵ (eg, truck drivers, elementary school teachers, airplane pilots) and those who live or work in hot conditions. Recently, armed services personnel stationed and working in a desert environment had low urine output despite intakes of fluids exceeding 17 L per day.⁷⁶ Individuals with urinary incontinence may limit their fluid intake in an effort to avoid publicly embarrassing situations. In these

situations, fluid goals and fluid intake schedules should be amended on a patient-by-patient basis. In the case of urinary incontinence, special attention in developing a plan may be required with respect to patients' emotional concerns and quality of life. There are a growing number of community-based or hospital-based urinary incontinence support groups, and providing information about these to the patient may be helpful. Collaboration with a health psychologist who could work with the patient to identify ways to achieve fluid goals might also be useful in this situation.

Hyperphosphaturia

As with calcium, urinary phosphorus excretion is not always related to nutritional intake because it is subject to homeostatic regulation involving parathyroid hormone, vitamin D, bone status, calcium status, and renal reabsorptive mechanisms.⁷⁷ Phosphorus is widely distributed in foods of both plant and animal origin. Patients with chronic kidney disease and whose circulating phosphorus concentrations are increased are managed multifactorially to reduce serum phosphorus, and this may include dietary restriction. However, the reduction of dietary phosphorus in stone formers to reduce risk for calcium phosphate stone formation is not widely practiced. In these patients, the control of urinary citrate, calcium, urine pH, and volume are of most importance.

Overweight/obesity are associated independently with increased risk for lithogenesis.⁷⁸ Because both are conditions of malnutrition, with or without concomitant genetic or metabolic contributors, nutrition therapy should address weight loss. Nutrition interventions can be highly successful in motivated individuals, and patients should be referred as needed to nutritionists with expertise and experience in weight-loss counseling.⁷⁹

SUMMARY

A tailored nutritional approach, targeted to patients' lithogenic risk factors, is recommended. There are some risk factors, observed in the 24-hour urine analysis, for example, which may not have a nutritional input and may not therefore be amenable to nutrition intervention. In part because of the complexity of studying nutrition and disease, evidence from appropriately designed studies may be lacking; yet nutrition therapy for kidney stone prevention is widely practiced. This article synthesizes best practice scenarios, most of which are evidence-based, for successful nutrition therapy against stone recurrence. An important concept stressed throughout is the need to

determine the cause of the observed risk factor(s) and to apply nutrition therapy accordingly.

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Imaging Techniques for Stone Disease and Methods for Reducing Radiation Exposure

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KEYWORDS

• Imaging • Nephrolithiasis • Computed tomography • Ultrasound • Radiation

KEY POINTS

- Imaging is a key component in the evaluation and management of patients with urolithiasis.
- Non-contrast computed tomography is considered the first line imaging study for the diagnosis of urolithiasis and provides critical information for operative planning.
- Beyond diagnosis, imaging provides important information that allows urologists to determine the most appropriate treatment modality for the patient. This information includes the size, location, and in some cases composition of stones.

INTRODUCTION

Imaging is a key component in the evaluation and management of patients with urolithiasis. Imaging allows for the rapid and definitive diagnosis of stones. Beyond diagnosis, imaging provides important information that allows urologists to determine the most appropriate treatment modality for the patient. This information includes the size, location, and, in some cases, composition of stones.

Historically, plain abdominal radiography (KUB) and excretory radiography (IVP) have been considered the studies of choice for the evaluation of patients with stones. These modalities have been largely supplanted by noncontrast computed tomography of the abdomen and pelvis (NCCT). Ultrasound has also been used in place of traditional radiography. Magnetic resonance imaging (MRI) has a limited role in the evaluation of patients with suspected urolithiasis.

Patients with urolithiasis are at risk for significant radiation exposure from imaging studies. Most of the radiation comes from NCCT. Plain radiography also exposes stone patients to radiation. Once diagnosed with a stone, a significant number of patients will undergo surgical intervention.

Fluoroscopy used during shock wave lithotripsy (SWL), ureteroscopy (URS), and percutaneous nephrolithotomy (PNL) contributes to the overall radiation exposure of patients with urolithiasis.

This article reviews currently available imaging modalities for the evaluation of urolithiasis. Methods to reduce radiation exposure to patients with stones are discussed as well.

Computed Tomography

Evaluation of renal colic

NCCT was first reported for the evaluation of urinary stones in the late 1970s.^{1,2} The initial indication for NCCT in the workup of urolithiasis was in diagnosing radiolucent stones.^{1–3} It was eventually demonstrated that NCCT had improved sensitivity for diagnosing ureteral stones in patients with flank pain compared with IVP.⁴ NCCT can be rapidly performed and does not require intravenous contrast. Unlike IVP, NCCT can identify stones of any composition, with the exception of stones formed by protease inhibitors, such as indinavir, which may not be visible on NCCT.⁵

Currently, NCCT is considered the first-line imaging study for the evaluation of the patient with acute flank pain and a suspected stone.⁶

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NCCT has a reported sensitivity of 95% to 98% and specificity of 96% to 98% for the diagnosis of a ureteral stone in a patient with acute flank pain (Table 1).⁷⁻⁹ Besides identifying the stone, NCCT allows for the evaluation of the signs of obstruction associated with ureteral stones. In patients with ureteral stones, NCCT was able to identify hydroureter in 82.7% of cases, hydro-nephrosis in 80% of cases, periureteric edema in 59% of cases, and unilateral renal enlargement in 57.2% of cases.¹⁰

When evaluating patients with acute flank pain, NCCT also has the ability to evaluate the rest of the abdominal and pelvic organs and possibly identify other causes of pain. In a series of 1000 consecutive NCCT performed for the evaluation of renal colic, an alternative diagnosis was made in 10.1% of the cases.¹¹ In another report reviewing the results of 1500 NCCT performed for the evaluation of flank pain with a suspected stone, 24% of the patients had an alternative CT finding without a urinary calculus.¹² In additional, another 7% had a completely negative CT. A urinary stone was identified in 69% of the patients, and of those patients with a stone, an additional pathologic condition was found in 47%.

Preoperative evaluation

Beyond the diagnosis of stones, NCCT is useful in the preoperative planning for the treatment of stones. Stone size and location are easily evaluated with NCCT. When planning SWL, the skin-to-stone distance can be determined on preoperative NCCT. This has been demonstrated to be an independent predictor of successful treatment with SWL.¹³⁻¹⁶ A skin-to-stone distance greater than or equal to 11 cm has been associated with worse stone-free outcomes for SWL when compared with skin-to-stone distances less than 11 cm.^{14,15} Prone NCCT can be useful

for the preoperative evaluation for planning prone percutaneous nephrolithotomy (PNL). Prone NCCT can determine the anatomic relations of adjacent organs and the pleura with upper pole calyces.^{17,18} This information can help determine the feasibility and risk of complication of an upper pole puncture during prone PNL.

Stone composition

Determining the stone composition preoperatively can also aide in deciding the best surgical modality to treat the stone. NCCT can provide information to aide in the determination of different stone types. Hounsfield units or CT attenuation has been frequently used to help identify stone composition.¹⁹ Harder stone types typically have higher attenuations. Calcium oxalate and brushite stones have been shown to have the highest CT attenuations, averaging more than 1400 HU. Uric acid stones typically have the lowest CT attenuation, on average 409 HU.¹⁹ A number of reports have demonstrated that the efficacy of SWL decreases with increasing stone attenuation as measured on NCCT.^{13,14,20,21} One series found that the rate of success for stone fragmentation was significantly lower in stones with a CT attenuation greater than 1000 HU when compared with stones with lower attenuation.²⁰ Another group reported a significantly higher effectiveness coefficient for SWL treating stones with attenuation less than 1200 HU versus those with greater than 1200 HU (80.4% vs 66.2%, *P* = .03).²¹ Finally, 2 reports have demonstrated that stone attenuation less than 900 HU is an independent predictor of SWL success.^{13,14}

Dual-energy NCCT is a novel technology that can be used to differentiate stones of different compositions more accurately.²²⁻²⁴ In an in vivo study, dual-energy NCCT was able to determine and differentiate stone compositions accurately,

Table 1 Sensitivity and specificity for identifying urolithiasis with different imaging techniques		
Imaging Technique	Sensitivity	Specificity
Noncontrast computed tomography	95%–98% ⁷⁻⁹	96%–98% ⁷⁻⁹
“Low-dose” CT	97% ⁷³	95% ⁷³
Ultrasound		
Renal stones	29%–81% ²⁵⁻²⁸	82%–90% ²⁵⁻²⁷
Ureteral stones	11%–93% ^{26,29-33}	87%–100% ^{26,29-33}
Plain radiography		
KUB	45%–58% ⁴⁴⁻⁴⁷	69%–77% ^{44,45}
IVP	85.2% ⁵³	90.4% ⁵³
Magnetic resonance imaging	93%–100% ⁵⁴⁻⁵⁶	95%–100% ⁵⁴⁻⁵⁶

including stones of mixed composition.²² Dual-energy NCCT has also been very effective in determining uric acid stone composition.

Ultrasound

Ultrasound is commonly performed during the evaluation of urolithiasis. The main advantage ultrasound has over other imaging modalities such as NCCT is that it is performed without any radiation exposure to the patient. However, ultrasound is not as sensitive or specific for the detection of renal or ureteral stones. The reported sensitivity of ultrasound for diagnosing renal stones ranges from 29% to 81%.^{25–28} The specificity ranges from 82% to 90%.^{25–27} The sensitivity of ultrasound for the detection of ureteral stones in patients with acute renal colic ranges from 11% to 93% and the specificity ranges from 87% to 100%.^{26,29–33}

Evaluation of renal colic

The sensitivity of ultrasound for the identification of a ureteral stone in a patient with renal colic is less than NCCT; however, it still plays a large role in evaluating patients with renal colic. Ultrasound, like NCCT, can be used to evaluate other abdominal or pelvic organs while concurrently imaging the urinary tract. This allows for identification of alternative diagnoses when evaluating for renal colic. One study comparing the sensitivity of ultrasound and NCCT for the diagnosis of a ureteral stone in patients with renal colic found that ultrasound had a significantly lower sensitivity compared with NCCT, 61% versus 96% ($P = .02$).³⁰ However, the sensitivity for ultrasound in determining any cause for the patient's symptoms, including hydronephrosis, stones, or appendicitis, was 85%. Another study comparing ultrasound and NCCT for the evaluation of renal colic found a 93% sensitivity for the diagnosis of a ureteral stone with ultrasound.³¹ In 6 of the 62 patients included in this study, ultrasound was able to find an alternative diagnosis: appendicitis, cholecystitis, cholelithiasis, adnexal mass, and torsed ovary.

When patients with renal colic are diagnosed with a distal ureteral stone with an NCCT, ultrasound can be effective at identifying the stone in the distal ureter during follow-up. One prospective study looked at the utility of ultrasound to follow up patients diagnosed with distal ureteral stones on an initial NCCT.³⁴ After their initial diagnosis, during follow-up the patients were imaged with ultrasound in addition to either repeat NCCT or radiography. The sensitivity of ultrasound on follow-up was 94.3% and the specificity was 99.1%.

Color Doppler ultrasound can be useful to improve the ability of ultrasound to detect ureteral stones. The “twinkling sign” on Doppler ultrasound appears as random color encoding in the area behind the stone where shadowing would be seen in traditional B-mode ultrasound. Doppler ultrasound using the “twinkling sign” has been shown to detect a higher percentage of stones than traditional gray-scale ultrasonography, 97% versus 66%.³⁵

Evaluation for obstruction

In patients with renal colic, ultrasound is excellent at identifying signs of ureteral obstruction. The sensitivity and specificity of ultrasound for the diagnosis of obstruction have been reported to be as high as 100%.³³ In 1 study looking at ultrasound for the evaluation of patients with confirmed renal colic, hydronephrosis was identified in 95% of cases, ureteral dilation in 89% of cases, and perirenal fluid in 23% of cases.³³

In addition to these signs of obstruction, the resistive index (RI) is a measure on color Doppler ultrasound that can improve the detection of ureteral obstruction in patients with renal colic.^{36–41} Ultrasound-determined RI has been shown to have a sensitivity of 88% and a specificity of 98% for ureteral obstruction, using IVP as the standard.³⁶ In this report, the RI in the obstructed kidneys were significantly greater than the RI in nonobstructed kidneys, 0.73 versus 0.64 ($P < .001$). In a prospective study, Doppler ultrasound with RI performed equally well when compared with NCCT for the detection of ureteral obstruction.³⁷ With IVP being the standard, the sensitivity and specificity for NCCT were 96% and 96% compared with 90% and 100% for Doppler ultrasound. Using an RI of 0.70 and a 10% difference in RI between kidneys as diagnostic of obstruction improves the sensitivity and specificity of ultrasound for the diagnosis of ureteral obstruction from 94.8% and 55.5% to 98.9% and 90.9%.³⁸ Doppler ultrasound can also identify ureteral jets, which can further aid in ruling out obstruction.^{40,41}

Limitations of ultrasound in the evaluation of urolithiasis

Ultrasound has limitations in the evaluation of urolithiasis and these are to stone location, size, and patient size. Ultrasound is not as sensitive at identifying stones in the ureter as it is in identifying stones in the kidney.^{25–33} One study evaluated 228 patients who underwent ultrasound for renal colic and suspected renal colic before ureteroscopy and found the sensitivity of ultrasound was 86.4% for identifying ureteral stones.⁴² Patients

in whom ultrasound failed to diagnose the stone had significantly smaller mean stone size (4 mm vs 6 mm, $P < .001$). In addition to being less sensitive at identifying smaller stones, ultrasound has been shown to overestimate stone size compared with NCCT.⁴³ In 1 report, ultrasound overestimated stone size by nearly 2 mm compared with NCCT.⁴³ The mean stone size on NCCT was 7.4 ± 4 mm versus 9.2 ± 5 mm on ultrasound ($P = .018$). Patient body habitus and body mass index (BMI) are other factors that can influence the accuracy of ultrasound. As the skin-to-stone distance increases, the discordance between ultrasound and NCCT for the measurement of stone size increases.⁴³ The ability of ultrasound to detect stones has been shown to be lower in patients with higher BMI.⁴²

Plain Radiography

Plain radiography of the abdomen/pelvis

Historically, KUB was the imaging modality of choice for the evaluation of urolithiasis. This was because most stones contained calcium and therefore would be expected to be visible on KUB. However, compared with NCCT and ultrasound, the sensitivity and specificity of KUB for detecting stones are poor. The sensitivity of KUB is reported to be 45 to 58%; the specificity is reported to be 69 to 77%.^{44–47} There are a number of factors that contribute to the reduced sensitivity and specificity of KUB, such as overlying bowel gas, extrarenal and extra-ureteral calcifications, and patient body habitus.⁴⁸

The use of tomography can improve the diagnostic accuracy of KUB for the evaluation of nephrolithiasis.⁴⁹ In 1 study evaluating KUB versus KUB with tomograms, 46% of patients had additional stones identified on tomograms. In 8% of patients, stones were only seen on tomograms.⁴⁹ The use of tomograms increases the amount of radiation the patient is exposed to. The effective doses for a KUB and each tomogram have been estimated to be 0.67 mSv and 1.1 mSv, respectively.⁵⁰ Therefore, if a KUB is performed with 3 tomograms, the total radiation exposure would be 3.97 mSv, greater than a low-dose NCCT.

KUB with ultrasound

KUB is useful as an adjunct to ultrasound in the evaluation of patients with renal colic. The sensitivity of ultrasound combined with KUB for the diagnosis of a ureteral calculus in a patient with renal colic has been reported to be as high as 96% with a specificity of 91%.⁵¹ When performed together, it is recommended that KUB be performed first to identify calcifications. Ultrasound can then be used to confirm that these

calcifications are in the urinary tract and therefore are stones.

Preoperative evaluation

KUB is useful in the preoperative evaluation before SWL. It can determine if a stone is radio-opaque and thereby seen with fluoroscopy. Obtaining a KUB can change the decision on how a stone is managed. One study reported that when a KUB is obtained after NCCT, the surgical management was changed in 17 of 100 patients based on information from the KUB.⁵² An NCCT scout image is not as sensitive for identifying stones compared with a KUB.^{46,47} Therefore, scout images from NCCT cannot be used as a surrogate for a KUB, and if SWL using fluoroscopy is planned, a KUB should be obtained preoperatively to determine if the stone will be visible on fluoroscopy during SWL.

Intravenous Pyelography

Before the advent of NCCT, IVP was considered the standard imaging technique for the evaluation of patients with renal colic. Currently, NCCT has largely supplanted IVP because of its superior sensitivity for detecting stones in these patients.^{4,53} In a prospective randomized trial comparing NCCT with IVP for the evaluation of acute flank pain, NCCT was demonstrated to have a sensitivity and specificity of 94.1% and 94.2% for identifying a stone compared with a sensitivity and specificity of 85.2% and 90.4% for IVP.⁵³

There are still some advantages of IVP in the evaluation of patients with urolithiasis. Because it is performed with contrast, IVP can provide information about renal function and whether a kidney is obstructed. Delayed images can be useful in evaluating ureteral anatomy for filling defects or strictures. It also provides detailed pelvicalyceal anatomy, which can be useful in planning surgical interventions, especially in those individuals with urinary tract anomalies. However, for these indications, IVP has largely been supplanted by CT with intravenous contrast or CT urograms.

Magnetic Resonance Imaging

There are limited indications for the use of MRI in the evaluation of urolithiasis. Although stones cannot be directly visualized using MRI, when evaluating patients with renal colic, MRI can detect signs of obstruction and can evaluate for alternative diagnoses. A number of different techniques and sequences have been reported for the evaluation of stones. The most common technique is to evaluate the T2-weighted images and assess

for signs of obstruction or look for filling defects, which may be stones.^{54–57} Using T2-weighted images, the findings of perirenal fluid and ureteral dilation had a sensitivity and specificity of 93% and 95% for the diagnosis of ureteral calculi in patients with renal colic.⁵⁶ Another group reported using a 3-dimensional fast low-angle shot (3D FLASH) sequence that requires the administration of gadolinium.⁵⁴ The sensitivity and specificity for the 3D FLASH sequence was 96.2% to 100% and 100% for the diagnosis of a ureteral stone. The 3D FLASH sequence combined with T2-weighted images has been shown to be as sensitive and specific for the diagnosis of ureteral stones as NCCT.⁵⁵ The addition of gadolinium for the 3D FLASH sequence can aide in the determination of stone size on MRI.⁵⁵

New Technology

Digital tomosynthesis

Digital tomosynthesis (DT) is a new imaging technology similar to KUB with tomograms. When DT is performed, a scout KUB is taken and then a single tomographic sweep over approximately 60° arc is done. A digital flat-panel detector records the data from the sweep and then software reconstructs the information to provide high-resolution “slice” or coronal images at varying depths (Fig. 1). This reconstruction

removes overlying structures such as bowel gas from slices, improving the resolution and visualization of stones. It also provides depth information. The depth information is useful in differentiating a calcification in the ureter versus an overlying transverse process from the spine (see Fig. 1).

There have been reports of the use of DT for the evaluation of urolithiasis.^{58,59} In 1 report, DT was compared with KUB with an additional plain film of the pelvis.⁵⁸ All patients underwent DT, KUB with the additional image of the pelvis, and NCCT, which was used as the standard. DT was superior to KUB for identifying intrarenal stones. The technology for DT can be used to perform an IVP, improving the image quality.⁵⁹ Two uro-radiologists reviewed both traditional IVP and IVP performed with DT. They evaluated the subjective diagnostic quality and found that 95.5% of the IVP with DT were of diagnostic quality versus 46.5% of the traditional IVPs. In addition, the dose of radiation was lower for the IVP with DT and they took less time. The dose of radiation from DT has been shown to be lower than that of a “low-dose” NCCT.^{50,58}

RADIATION REDUCTION

Radiation exposure from medical sources has been steadily increasing over the past 3 decades. In 1980, the per capita radiation exposure in the

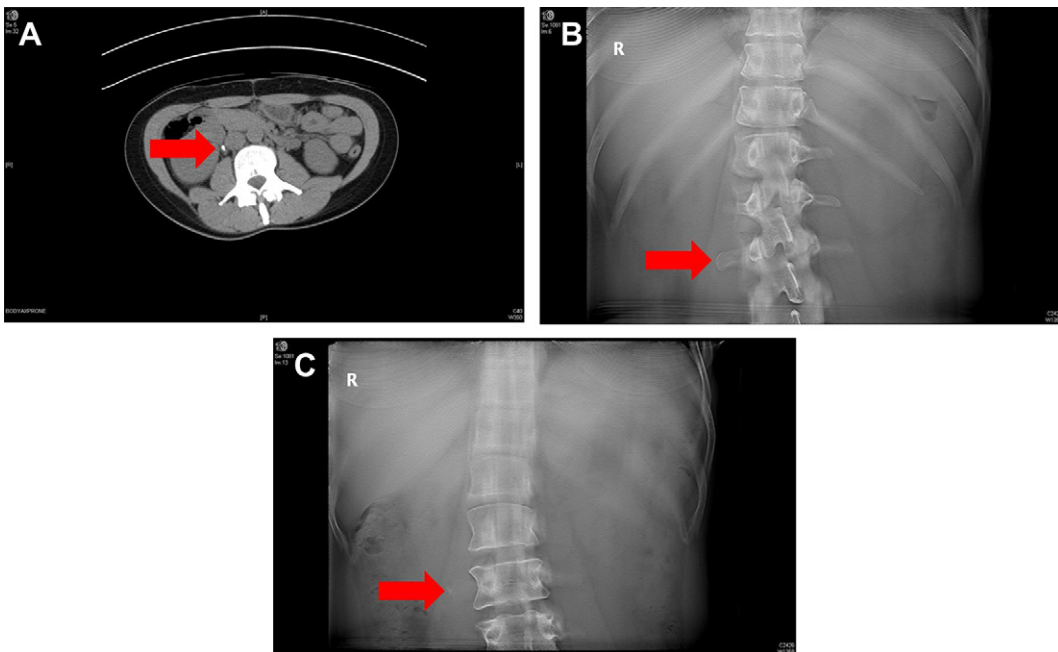


Fig. 1. (A) NCCT demonstrated a right mid ureteral stone. Arrow points to the stone. (B) Coronal “slice” from digital tomosynthesis demonstrated a spinal transverse process. Arrow points to spinal transverse process (C) Anterior coronal “slice” from digital tomosynthesis demonstrating the ureteral stone. Arrow points to the ureteral stone.

United States from medical sources was 0.54 mSv.⁶⁰ In 2006, this increased nearly 600% to 3.0 mSv. Most of this increase was from the use of CT scans. In 2006, there were an estimated 62 million CT scans performed in the United States.⁶¹ It is estimated that an additional 29,000 cancers could be related to CT scans performed in the United States in 2007.⁶²

Patients with urolithiasis are at increased risk for significant radiation exposure from diagnostic imaging, specifically NCCT. From 1996 to 2007, the use of NCCT to assess patients with suspected stones increased significantly from 4% to 42.5%.⁶ The use of NCCT for the evaluation of flank pain in the emergency room has increased significantly from 19.6% to 45.5% of patient visits over the past decade.⁶³ It has been reported that patients undergo a median of 1.7 NCCT in a 1-year period following an acute stone episode.⁶⁴ Of the 108 patients included in this study, 94 (87) went on to have a surgical intervention. Fluoroscopy used during these surgical interventions also contributes to these patients' overall radiation exposure. Given that patients with urolithiasis constitute a high-risk population, measures to reduce the amount of radiation these patients are exposed to are extremely important.

Study Selection

Proper selection of imaging studies for the evaluation of urolithiasis is an important way to reduce radiation. Whenever possible, radiation-free techniques such as ultrasound or MRI should be used. Ultrasound should be considered the first-line imaging study for the evaluation of stones or renal colic in pediatric patients and pregnant women. The use of MRI has also been reported for the evaluation of renal colic in pregnant women.⁶⁵ Both of these modalities have high sensitivity for diagnosing ureteral obstruction.^{33,36–41,54–57} The combination of ultrasound and KUB has been shown to have high sensitivity for the diagnosis of ureteral stones and exposes patients to less radiation than an NCCT.⁵¹

The American Urological Association recently submitted guidelines regarding appropriate imaging selection for the evaluation of ureteral calculi.⁶⁶ The authors recommend "low-dose" NCCT as the initial imaging modality for a patient with flank pain and a suspected ureteral stone if the BMI is less than 30 kg/m² and a standard-dose NCCT if the patient is obese. They recommend a KUB concurrently with the NCCT if the stone is not seen on the scout image. For follow-up of radio-opaque stones, they recommend ultrasound along with KUB. In cases of radiolucent

stones, they recommend follow-up imaging with NCCT.

Low-dose computed tomography

Although ultrasound and MRI can be used for the evaluation of patients with urolithiasis, NCCT has the highest sensitivity and specificity for the diagnosis of stones. NCCT also is very valuable for preoperative planning. The amount of radiation a patient is exposed to from an NCCT of the abdomen and pelvis is dependent on the protocol and machine used, as well as patient characteristics. For a standard NCCT of the abdomen and pelvis performed for the evaluation of stones, the effective dose has been reported to be as high as 9.6 mSv for men and 12.6 mSv for women.⁶⁷

With the advent of new CT scanner technology and new software, NCCT for the evaluation of urolithiasis can be performed with lower radiation doses while maintaining diagnostic accuracy. These "low-dose" CT scans can greatly reduce the amount of radiation patients are exposed to. There is no standard definition for "low-dose" CT. A recent meta-analysis evaluating the performance of low-dose CT for the diagnosis of urolithiasis defined low-dose CT as applying an effective dose less than 3 mSv for the entire examination.

There have been a number of reports assessing the effectiveness of low-dose CT for the evaluation of stones and renal colic.^{67–72} One report compared a standard NCCT at a dose of 7.3 to 10 mSv versus a low-dose NCCT at 1.4 to 1.97 mSv for the evaluation of acute renal colic.⁷¹ Low-dose NCCT had equivalent sensitivities to standard NCCT for the diagnosis of ureteral stones with the exception of ureteral stones less than 2 mm. In these cases, the sensitivity of low-dose NCCT was 68% to 79% versus 95% sensitivity for the standard-dose NCCT.⁷¹

In another evaluation of low-dose versus standard-dose NCCT for the evaluation of acute renal colic, low-dose NCCT achieved sensitivities and specificities for diagnosing a stone or indirect signs of a stone approaching standard-dose NCCT.⁶⁷ Compared to standard-dose CT, low-dose NCCT had a sensitivity of 97% and a specificity of 98% for identifying at least 1 direct or indirect sign of a ureteral stone. The authors in this trial did report decreased sensitivity and specificity for the diagnosis of ureteral calculi with patient BMI greater than 30 kg/m², 50% and 89%, respectively, compared with 95% and 97% in non-obese patients.⁶⁷ A recent meta-analysis of studies evaluating low-dose NCCT demonstrated a pooled sensitivity of 97% and a specificity of 95%.⁷³

Low-dose NCCT has been shown to be useful for the follow-up of recurrent stone formers to

evaluate for new stone formation or stone growth.⁷⁰ Even at a dose reduction of 56%, the authors reported no significant intraobserver or interobserver differences for the detection of urolithiasis. Low-dose CT has also been reported for the evaluation of renal colic and flank pain in pregnant patients with high sensitivity and specificity.⁷⁴

Low-dose NCCT appears to perform as well as standard NCCT for the evaluation of urolithiasis and, in cases where NCCT is to be performed; low-dose NCCT should be considered the first-line imaging study.

FLUOROSCOPY

Fluoroscopy is commonly used during surgical procedures to treat patients with urolithiasis including SWL, URS, and PNL. Therefore, patients who undergo treatment of stones are exposed to even more radiation. The amounts of radiation patients are exposed to during PNL and URS have been quantified using a validated model.^{75,76} At 1 institution, nonobese patients undergoing PNL were exposed to a median 9.34 mSv for a left-sided procedure and 7.11 mSv for a right-sided procedure.⁷⁵ Nonobese patients undergoing URS were exposed to a median of 1.13 mSv.⁷⁶ There are a number of methods to reduce the amount of radiation patients are exposed to in the operating room.

As Low as Reasonably Achievable

The principle of *As Low As Reasonably Achievable* (ALARA) should always be applied when using fluoroscopy. This includes collimating the image as much as possible and placing the image intensifier as close to the patient as possible.⁷⁷ Pulsed fluoroscopy should be used at the lowest possible frames per second that provides usable image quality to perform the procedure. Last image hold should be used to save and transfer images to an adjacent screen to be used as a reference during the procedure. Close adherence to the principles of ALARA has been demonstrated to reduce radiation dose during pediatric interventional radiology procedures.⁷⁸

Radiation Reduction During PNL

When performing a retrograde pyelogram to aide in fluoroscopic access during PNL, the use of air instead of iodinated contrast may reduce radiation exposure. A retrospective review of 96 PNL procedures demonstrated that the use of air reduced radiation exposure nearly 50% when compared

with contrast, 4.45 mSv versus 7.67 mSv ($P = .001$).⁷⁹

The use of ultrasound to obtain access also can reduce radiation exposure by reducing or eliminating the need for fluoroscopy. There have been a number of reports on the use of ultrasound to aide in access during PNL.^{80–85} Two randomized controlled trials have been performed comparing PNL with ultrasound combined with fluoroscopy versus fluoroscopy alone.^{83,84} In the first trial, the authors report that access took significantly longer with ultrasound, 11 minutes versus 5.5 minutes ($P < .0001$). However, the fluoroscopy time was significantly longer in the patients who had their entire procedure performed with fluoroscopy (41.4 seconds vs 57.0 seconds, $P = .0001$). The second trial demonstrated shorter time to successful puncture in the ultrasound group (1.8 minutes vs 3.2 minutes, $P < .01$) and significantly shorter fluoroscopy time with the use of ultrasound (14.4 seconds vs 28.6 seconds, $P < .01$).⁸⁴

Although these trials demonstrated a reduction in fluoroscopy time with ultrasound, the patients were still exposed to a small amount of radiation from fluoroscopy.^{83,84} The ideal situation to reduce radiation exposure would be to eliminate fluoroscopy altogether. Studies have demonstrated the feasibility and safety of performing PNL with ultrasound alone in a select patient population.^{80,81} In 1 series, 47 patients with a solitary stone located in the renal pelvis associated with mild-to-moderate hydronephrosis were treated with PNL using ultrasound alone.⁸⁰ The mean stone size was 31.5 mm and the stone-free rate was 83%. In 2 morbidly obese patients, fluoroscopy was needed to aide in access. The second series reported on 34 patients with a solitary renal pelvic stone.⁸¹ The mean stone size was 24 mm and a single lower pole puncture was obtained in all cases. The stone-free rate was 94%. The use of ultrasound to perform PNL without fluoroscopy seems to be safe and efficacious in a select group of patients.

Radiation Reduction During URS

The same principles of ALARA apply to fluoroscopy use during URS. In addition, there have been reports on methods to reduce fluoroscopy time for URS. One group of investigators demonstrated a 24% reduction in fluoroscopy time when surgeons were given periodic reports documenting their mean fluoroscopy time compared with that of their peers.⁸⁶ In addition, intraoperative techniques have been reported to reduce fluoroscopy time during URS.⁸⁷ These measures include the use of a laser-guided C-arm, tactile cues for the placement of guidewires, stent placement

under direct vision through a cystoscope, use of a designated fluoroscopy technician, and single pulse fluoroscopy mode for portions of the case. When these measures were implemented, the authors reported a reduction in the mean fluoroscopy time during URS from 86.1 seconds to 15.5 seconds.

Radiation Reduction During SWL

The principles of ALARA apply to the use of fluoroscopy during SWL as well. In addition, ultrasound can be used to target the stone instead of fluoroscopy with good success.⁸⁸

SUMMARY

Imaging plays an important role in the evaluation of patients with urolithiasis. NCCT of the abdomen and pelvis is the most sensitive and specific imaging modality for diagnosing stones. Images from NCCT also play an important role in determining the best surgical approach to treat a stone. When NCCT is performed for the evaluation of stones, a "low-dose" protocol should be used to reduce the amount of radiation these patients are exposed to whenever possible. Ultrasound is also useful in the evaluation of urolithiasis. Ultrasound should be considered first-line imaging for stones in pediatric and pregnant patients. Ultrasound has decreased sensitivity and specificity for identifying stones compared with NCCT; however, it has nearly equivalent sensitivities and specificities for diagnosing obstruction. Plain abdominal radiography is mostly useful for preoperative planning before SWL and as an adjunct to ultrasound. The role of MRI in the evaluation of urolithiasis is limited.

Stone patients are exposed to significant amounts of radiation from diagnostic imaging, primarily NCCT, and fluoroscopy in the operating room. Proper imaging modality selection helps to minimize radiation exposure. Following the principles of ALARA in the operating room can help reduce the amount of radiation patients are exposed to from fluoroscopy.

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Shockwave Lithotripsy–New Concepts and Optimizing Treatment Parameters

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KEYWORDS

• Radiodensity • Lithotripsy • Kidney stones • ESWL • Acoustic coupling and focus zone

KEY POINTS

- Stone radiodensity and skin to stone distance can both be used to optimize extracorporeal shock wave lithotripsy (ESWL) outcomes.
- The importance of acoustic coupling cannot be overemphasized. Air pockets within coupling gel can significantly reduce ESWL efficiency.
- ESWL outcomes are maximized using a frequency of 60 shock waves per minute compared with 120 shock waves per minute.
- Power ramping with a brief pause can not only improve ESWL stone fragmentation outcomes but also decrease renal tissue injury.
- Lithotripters with larger focal zones have superior stone fragmentation rates along with better renal safety profiles.
- Improved acoustic feedback and stone monitoring systems, as well as residual stone fragment clearance techniques, are being developed that will further improve the stone fragmentation outcomes of ESWL.

INTRODUCTION

The treatment of kidney stone disease has changed dramatically over the past 30 years. This change is due in large part to the arrival of ESWL. Before the advent of ESWL in the early 1980's, most kidney stones were treated with open surgery. ESWL along with the advances in ureteroscopic and percutaneous techniques has led to the virtual extinction of open surgical treatments for kidney stone disease.

The first successful ESWL treatment was accomplished in 1980 in Germany by Dr Christian Chaussy using a Dornier HM1 lithotripter. Owing to its effectiveness and its rare side effects, ESWL was quickly approved by the US Food and Drug Administration (FDA) for clinical use. Dr James

Lingeman using the unmodified Dornier HM3 lithotripter performed the first ESWL procedure in North America. Since then, ESWL has been used with increasing frequency to treat more and more complex stones. Multiple sources have confirmed that kidney stone disease is on the rise, and as a result, surgical treatments for these kidney stones are also on the rise.^{1–5} Turney and colleagues⁶ have recently shown that over the past decade, ESWL for upper tract stones has increased by 55%. Most of this increase was caused by ESWL performed on kidney stones (69% increase). ESWL performed on the ureter remained stable. With the increase in stone disease, surgical treatment must not only be effective but also be efficient.

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Initial work with ESWL was very optimistic because it was reported to be extremely effective even when applied to complex stone cases.⁷⁻⁹ Furthermore, this noninvasive technique was found to have very few side effects. With the increasingly widespread acceptance and use of ESWL, it was discovered that this procedure was associated with a few important limitations. Some urinary stones were found to be resistant, and their fragmentation could not be accomplished consistently using ESWL.¹⁰⁻¹² Also, some renal stones that could be fragmented would not fragment completely and secondary treatments were necessary. In addition, renal anatomy (calyceal diverticulum or acute infundibulopelvic angles) and location (lower pole calyx) of the stone were crucial to ESWL stone-free outcomes.¹³ Finally, many reports have demonstrated the frequent minor complications and the rare major complications.^{14,15}

For the reasons stated above, much research has gone into understanding how ESWL can be made more efficient and safe. This article discusses the parameters that can be used to optimize ESWL outcomes as well as the new concepts that are affecting the efficacy and efficiency of ESWL.

OPTIMIZING PARAMETERS

Numerous parameters can be used to optimize ESWL outcomes. These parameters include stone characterization, acoustic coupling, and shock wave rate and sequence.

Stone Characterization

One of the main drawbacks of ESWL is its inability to fragment certain types of stones. This drawback is extremely important because patients who harbor these types of stones will be subjected to ESWL and will thus be exposed to its complications (minor and major) without the achievable benefit of fragmentation. In addition, failure of stone fragmentation will lead to secondary treatments, which will increase medical costs. The stones most resistant to ESWL include brushite, calcium oxalate monohydrate, and cystine.¹⁰⁻¹² Therefore, if one could predict the type of stone, then the likelihood of that stone being fragmented by ESWL could be predicted. Numerous studies have demonstrated that noncontrast computed tomography (NCCT) can be used to measure differences in radiodensity, which can be used to distinguish between different types of stones.¹⁶⁻²⁰ More recently, studies have shown that preoperative NCCT can be used to predict the likelihood of stone fragmentation.²¹⁻²⁶ El-Assmy and colleagues²¹ demonstrated that stones with Hounsfield units (HU) greater than 1000 required a statistically significant

higher number of shock waves to be fragmented. Also, Wang and colleagues²³ concluded that stone densities greater than 900 HU were a significant predictor of ESWL failure.

Along with the type of stone, the distance of the stone from the patient's skin can have a significant impact on the likelihood of stone fragmentation. Numerous studies have shown that the distance of the stone from the skin, also known as the skin to stone distance (SSD) can be used as an indicator of the likelihood of stone fragmentation.²⁷⁻²⁹ SSD is measured by averaging 3 fixed distances from the stone to the skin. These 3 measurements include 1 horizontal, 1 vertical, and 1 diagonal measurement from the stone to the skin. Pareek and colleagues²⁷ found SSD to be a statistically significant predictor of ESWL failure when it was greater than 10 cm. In 2009, Patel and colleagues²⁹ found that patients with an average SSD of 10.7 cm had a statistically significant higher rate of residual stone after ESWL compared with those who had an average SSD of 8.3 cm.

As both SSD and stone radiodensity have been demonstrated to be independent predictors of stone fragmentation by ESWL, Perks and colleagues²⁸ used both these factors to evaluate their combined ability to predict stone fragmentation by ESWL. In this retrospective study on 111 patients, Perks and colleagues²⁸ found that stones with a radiodensity of less than 900 HU combined with an SSD of less than 9 cm predicted ESWL success, an observation that was independent of stone size, location, or body mass index.

As mentioned previously, cystine calculi are extremely hard to fragment with ESWL. Kim and colleagues¹⁰ evaluated the hypothesis that cystine stones with specific morphologies might be easier to fragment with ESWL. This study demonstrated that cystine stones with a "rough" morphology contained void regions that are visible on NCCT. The investigators concluded that cystine calculi that appeared homogenous on NCCT required 61% more shock waves for fragmentation than did stones that appeared heterogeneous.

In summary, careful attention to stone characterization, including SSD and stone radiodensity, can be used to accurately select patients who have a greater possibility of having their stones fragmented using ESWL. This ability will translate into fewer secondary treatments, which will cut down on medical costs.

Acoustic Coupling

Over the past 30 years, ESWL has gone through numerous changes with the ultimate goal of

complete and universal stone fragmentation with minimal side effects. Much research has gone into the achievement of this goal. One parameter that has recently undergone reevaluation is acoustic coupling. The HM3 uses water as a medium for coupling, which has been found to be ideal. This is because body tissue has an acoustic impedance very close to that of water, and therefore, a shock wave generated in water will pass into the body with minimal reflection or absorption of energy at the water–skin interface. Unlike the Dornier HM3, modern lithotripters have incorporated dry head energy sources that have treatment heads that are brought into contact with the patient. At present, the only machine that does not have a “dry head” is the Storz SLX (Storz Medical AG, Tägerwil, Switzerland), which uses a partial water bath for coupling. Typically, gel is used to couple the dry head lithotripters to the skin of the patients. Once the gel is applied, the head of the lithotripter is brought into contact with the patient’s skin. An important potential problem of gel coupling is the introduction of air pockets into the gel. These air pockets, which are often abundant, have a deleterious effect on shock wave propagation. Shock waves travel well through water and coupling gels, but not through air.

In 2006, Pishchalnikov and colleagues³⁰ demonstrated a negative relationship between increasing air pockets and ESWL efficiency. More specifically, using a Dornier DoLi-50 electromagnetic lithotripter, this *in vitro* study established that with as little as 2% of the coupling area covered with air pockets, there was a reduction in stone breakage by 20% to 40%. Jain and colleagues³¹ found that optimal fragmentation was obtained using bubble-free ultrasound gel. In addition, Bergsdorf and colleagues³² demonstrated in a clinical study that gel with lower viscosity and better quality provided significantly better stone fragmentation. Finally, in a study by Neucks and colleagues³³ it was discovered that the quality of coupling can be improved by the way the gel is handled and applied. The most effective way to apply coupling gel is to place it directly from the container as a mound to the center of the treatment head. Then, without spreading it around, the treatment head should be pressed against the patient.

The importance of acoustic coupling through gel application cannot be overemphasized. It is paramount that air pockets be limited so that shock waves can be delivered with the greatest efficiency. If coupling is overlooked, ESWL becomes less effective, leading to inferior outcomes and the need for increased secondary treatments.

Shock Wave Rate

Another important parameter that has a significant impact on ESWL outcomes is the rate at which shock waves are delivered. *In vitro* work first reported that slowing the rate at which shock waves are delivered can have a major impact on both stone fragmentation and acute renal tissue damage.³⁴ Numerous prospective clinical trials have confirmed that ESWL stone fragmentation outcomes are improved at 60 shock waves per minute compared with the standard 120 shock waves per minute.^{35–38} Porcine models have also demonstrated that acute renal injury can be reduced at 60 shock waves per minute.^{39,40} A meta-analysis by Semins and colleagues³⁵ showed that a treatment performed at a rate of 60 shocks per minute is associated with a higher rate of treatment success than treatment performed at a rate of 120 shocks per minute. One drawback of slowing the rate of shock wave delivery is the increased time required to break urinary calculi, which may extend the time that the patient is subjected to sedation.

One hypothesis proposed for the decreased stone fragmentation with an increased shock wave rate was an increase in the formation of cavitation bubbles, which would interfere with the transmission of the positive pressure phase of shock waves. However, Pishchalnikov and colleagues⁴¹ proposed an alternative explanation suggesting that the main reason was actually the loss of the negative pressure portion of the shock wave and not the interference with the positive pressure portion.

In summary, many studies have confirmed that ESWL outcomes are maximized using a frequency of 60 shock waves per minute compared with 120 shock waves per minute. These outcomes include a higher rate of stone fragmentation as well as a decreased rate of renal tissue damage.

Shock Wave Sequence

The last ESWL parameter to consider, which can have a dramatic impact on ESWL outcomes, including stone fragmentation and effect on acute renal tissue injury is the sequence that is used to deliver the shock waves. Sequence refers to the timing of shock waves and the number of shock waves given at a specific power level. Power ramping refers to the delivery of several shock waves at lower power levels before getting to the desired treating power level. Most centers treating under sedation perform some form of power ramping to help the patient get accustomed to the shock waves.

In vitro studies on pigs, power ramping has been shown to enhance stone breakage.^{42–44}

In vitro studies using the Dornier HM3 lithotripter demonstrated that progressively increasing the output voltage can produce superior stone comminution.⁴² It has also been confirmed that stepwise power ramping can significantly decrease renal injury.^{45–47} In a porcine model, treatment with 100 shocks at 18 kV followed by 2000 shocks at 24 kV significantly decreased acute renal lesion sizes compared with 2000 shocks at 24 kV. It was thought that the key to the protective effect in power ramping was a brief pause (roughly 3 minutes) between the lower and higher power settings.⁴⁷ However, more recently Handa and colleagues⁴⁸ confirmed that renal protection can be achieved without instituting a pause in ESWL treatment but that a ramping protocol is, however, necessary.

Therefore, power ramping with a brief pause can not only improve ESWL stone fragmentation outcomes but also decrease renal tissue injury and should be incorporated into all ESWL protocols.

In conclusion, optimizing parameters including SSD, stone radiodensity, acoustic coupling, reduced shock wave rate, and power ramping can and should always be applied when performing ESWL. Application of these will not only improve stone fragmentation but also decrease renal tissue injury. These simple yet effective techniques will reduce, if not eliminate, the need for secondary procedures, which will in turn reduce medical costs.

NEW CONCEPTS

With the tremendous amount of research being done in ESWL, more and more new concepts are being investigated. This section concentrates on these newer concepts including small versus large focal zone lithotripters, tandem and dual head lithotripters, acoustic feedback systems, stone monitoring systems, and residual fragment clearance techniques.

Small versus Large Focal Zone Lithotripters

ESWL acoustic energy is focused on to a relatively small zone surrounding the focal point of the lithotripter. The focal point is a geometric point and is usually the location of the kidney stone of interest. The focal zone can be either small or large, and the amount of energy or peak pressure that is applied to it can be manipulated. This relationship is also known as the acoustic output, which is the amplitude and spatial distribution of the acoustic energy delivered to a specific focal volume. The original Dornier HM3 produces peak positive pressures of about 40 MPa on a focal width of about 10 to

12 mm. Most modern lithotripters generate higher pressures between 60 and 160 MPa delivered to a more narrow focal width of 3 to 6 mm. The XX-ES CS-2012A (Xi Xin Medical Instruments Co. Ltd, Suzhou, China) and the LithoGold LG-380 (Tissue Regeneration Technologies, Woodstock, GA, USA) produce low pressures (roughly 20 MPa) with broad focal zones (roughly 18–20 mm).

In vitro studies have demonstrated that a larger focal zone can improve stone breakage.⁴⁹ Owing to respiratory movements, urinary stones are in continual motion. It is hypothesized that the stone will have a greater chance of staying within the target focal zone if the zone is larger. Pishchalnikov and colleagues⁵⁰ demonstrated this hypothesis in an in vitro study. Furthermore, lithotripters with tighter focal zones tend to have fewer shock waves that actually hit the stone and more shock wave energy that is deposited directly into renal tissue.⁵¹ This mechanism is not the only one by which large focal zone lithotripters improve stone breakage. Focal width also seems to have a crucial role in the mechanism of stone comminution. Numerical modeling studies have shown that shear waves necessary to cause large internal stresses are enhanced when the focal width is larger than the diameter of the stone.^{52,53}

An important aspect of ESWL is safety, and numerous studies have shown that the use of a tighter focal zone with higher peak pressures is associated with not only a higher retreatment rate but also a higher rate of side effects when compared with a wider focal width.^{54–58} Porcine models using treatment protocols recommended by both the XX-ES CS-2012A and the LG-380 broad focal zone lithotripter machines produce minimal renal lesions.^{59,60}

Tandem and Dual Head Lithotripters

Tandem head lithotripters

As ESWL progresses, more and more research is being focused on ways of improving the fragmentation of stones. In light of this, efforts have been made to enhance one of the key mechanisms of stone breakage. Cavitation bubbles are an essential part of stone comminution, and a novel idea is to use 2 shock waves in rapid succession to drive the forceful collapse of bubbles against the stone. This method of stone breakage has been achieved by 2 methods. One is to add an auxiliary piezoelectric array to generate a second shock wave along the same axis as the first shock wave.^{61–63} This method has led to significant improvements in stone comminution in vitro.⁶² The other method is to fit a piezoelectric lithotripter with an additional charging and discharge circuit to produce

a second pulse. Fernandez and colleagues⁶⁴ found clinically that this technique did not increase the efficiency of fragmentation but that it did significantly decrease the time required to fragment the stone.

Dual head lithotripters

Dual head lithotripters deliver closely timed shock waves from different treatment heads that are aligned to the exact same focal point.^{65,66} Initial reports suggest that these machines can be safe and effective.^{67,68}

Acoustic Feedback Systems

The main disadvantages of ESWL are the inefficiency side effects associated with it. These disadvantages are interrelated in that excess shock waves are commonly applied in an effort to assure stone breakage and ESWL effects on tissue are related to the shock wave dose. Recent research has demonstrated the possible role for an acoustic feedback system to monitor stone fragmentation.⁶⁹ This acoustic feedback system uses a broadband receiver to monitor shock waves and reverberations from the acoustic wave transmitted into the stone. As the stone fragments, reverberations from smaller fragments generate higher frequency signals. In vitro studies have demonstrated the feasibility of this system to discriminate between fragments that differ in size by only 1 to 2 mm.⁶⁹ This system allows the urologist to know when the stone is fragmented and therefore reduces excess or unnecessary shock waves to the renal tissue.

Stone Monitoring Systems

Once a stone has been localized, its movement in and out of the focal zone affects fragmentation. The longer the stone remains within the focal zone, the more likely it is to fragment. Maintaining the stone in the focal zone is challenged by respiratory motion. Depending on the patient's respiratory rate, the stone can be outside the focal zone during 50% or more of the administered shock waves.⁵¹ This movement translates to more shock wave energy missing the stone and hitting renal tissue instead.

Several targeting systems have been developed to track stones during ESWL. These systems use ultrasound imagers, tracking algorithms, and piezoelectric lithotripters with built-in systems to continually locate the stone before shock wave firing.^{70–72} Although these systems show promise, none of them are currently being used in the clinical setting.

Residual Fragment Clearance Techniques

ESWL has been proved to be an excellent treatment of renal stone disease. However, one of its main limitations is the clearance of residual fragments, which will often lead to secondary treatments. This drawback is especially important for lower pole calculi that are subjected to ESWL. Numerous methods of residual fragment clearance have been proposed including percussion, diuresis, and inversion therapy.^{73–75} The success of these methods of residual stone fragment clearance have been limited.

There has been recent research in the domain of focused ultrasound technology directed at residual stone fragment clearance, and it shows great promise.⁷⁶ Shah and colleagues⁷⁶ recently demonstrated the use of focused ultrasound technology in a study involving live porcine models implanted with human stones. With this technology they were able to expel calculi effectively and safely from the kidney in their animal model. This technology could hold promise in the clearance of residual fragments after ESWL.

SUMMARY

Over the past 30 years, treatment of renal stone disease has changed dramatically. Treatments have become more and more minimally invasive. The only entirely noninvasive treatment remains ESWL. However, limitations to ESWL have been identified and have led to more emphasis on other treatment modalities. In an effort to return to noninvasive therapy, ESWL must improve. Therefore, with the incorporation of optimizing parameters, ESWL can become more efficient and safer. In addition, new concepts, novel ideas, and future research are leading the way toward a brighter future for ESWL.

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Advances in Ureteroscopy

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KEYWORDS

• Ureteroscopy • Endourology • Laser • Lithotripsy • Stone • Basket • Technology • Advances

KEY POINTS

- Several digital ureteroscopes have been introduced over the past few years.
 - Benefits of digital ureteroscopes include larger, clearer images with a decreased need for accessory equipment.
 - Disadvantages include a larger tip diameter and increased baseline cost.
- Holmium laser lithotripsy remains the most common method of stone fragmentation during ureteroscopy, and there are increasing efforts in adapting technology to prevent laser damage to the scope.
- Hybrid guidewires are the most popular guidewires, yet several types are available with different indications for use depending on the scenario.
- Nitinol stone baskets have replaced stainless steel ones and they are now available at very small sizes as thin as 1.3F.
- Numerous antiretropulsion devices are now available, each with novel methods of preventing proximal stone migration during ureteroscopy and lithotripsy.

INTRODUCTION

Over the past 3 decades, endourology has undergone a remarkable evolution with the advent and incorporation of new technologies. The development of smaller, more flexible ureteroscopes, higher-definition cameras, and a wide variety of novel instruments have changed the role of the field from one of diagnostics to one of treatment. In this review, the authors highlight the latest technological achievements in ureteroscopy.

FLEXIBLE URETEROSCOPES

Advancements in flexible ureteroscopes have had perhaps the greatest impact in changing endourology. Smaller sizes and increased capabilities in terms of optics, deflection, and instrumentation

have now made it possible to access the entirety of the urinary tract. The rate of technologic improvement in this field has been staggering, with new ureteroscopes introduced each year (**Table 1**). Representations of the deflection characteristics and tip appearances of some of the newer flexible ureteroscopes can be seen in **Figs. 1** and **2**.

One of the most significant changes has been a change from fiberoptic to digital imaging. This change has been made possible through the advancement and miniaturization of the charge couple device and complementary metal oxide semiconductor image sensors. These chips are now small enough to be directly incorporated at the tip of the ureteroscope creating the so-called *chip on the stick* scope. Such technology eliminates the need for internal optics within the shaft of the scope potentially allowing for more durable

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Table 1 Currently available flexible ureteroscope models							
Manufacturer	Model	Digital	Tip Diameter (F)	Proximal Diameter (F)	Channel Size (F)	Deflection (Up/Down) (Degrees)	Length (cm)
Karl Storz (Tuttlingen, Germany)	Flex- X ²	No	7.5	8.5	3.6	270/270	67.5
Karl Storz	Flex-Xc	Yes	8.5	8.5	3.6	270/270	70
Olympus (Tokyo, Japan)	URF-P5	No	5.4	8.4	3.6	180/275	70
Olympus	URF-V	Yes	8.5	9.9	3.6	180/275	67
Olympus Gyus ACMI (Southborough, Massachusetts)	DUR-8E	No	6.75	10.81	3.6	170/180	64
Olympus Gyus ACMI	DUR-D	Yes	87.0	9.3	3.6	250/250	65
Stryker (Stryker Inc, Portage, MI)	Flexvision U-500	No	6.9	—	3.6	275/275	64
Wolf (Richard Wolf, Knittlinton, Germany)	Viper	No	6.0	8.8	3.6	270/270	68
Wolf	Cobra	—	6.0	9.9	3.3	270/270	68

deflection mechanisms and equipment overall.¹ An additional advantage is eliminating the need for several pieces of equipment, including a separate camera; camera cord; light source or light

cord; and several cumbersome steps, such as focusing and white balancing.² Furthermore, without the need for fiberoptic bundles within the shaft, larger working channels can be used.³ Although

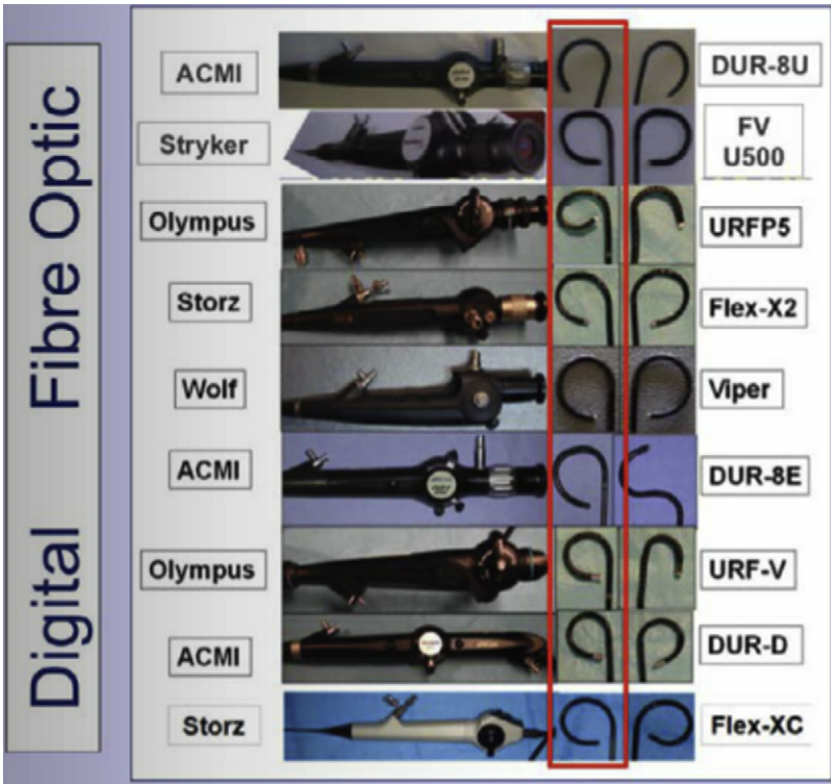


Fig. 1. Deflection characteristics of currently available flexible ureteroscopes. (From Traxer O. Digital and video flexible ureterorenoscopes: the future is now. AUA News 2012;17(7):1–9; with permission.)

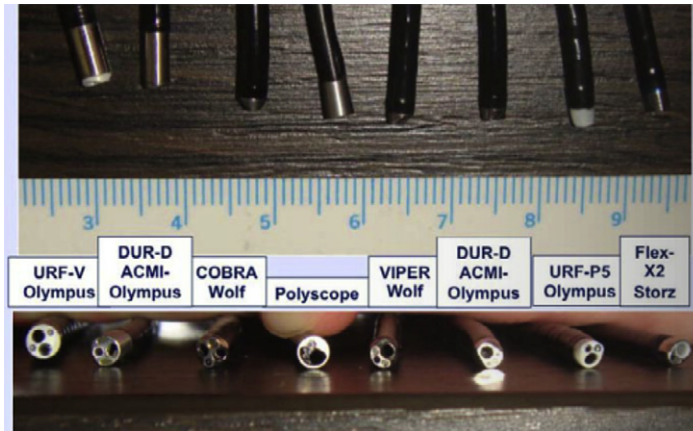


Fig. 2. Distal tips of currently available flexible ureteroscopes. (From Traxer O. Digital and video flexible ureterorenoscopes: the future is now. AUA News 2012;17(7):1–9; with permission.)

promising, the improvements do come at the expense of a larger-tip diameter, generally 8F or greater, making passage into narrow areas slightly more challenging. Additionally, the use of these scopes occasionally requires prestenting the ureter, ureteral balloon dilation, or the concomitant use of a ureteral access sheath to obtain access.

The image obtained with a digital scope is generally larger and clearer than that obtained with traditional fiberoptic scopes. Additionally, there is no honeycomb/pixelation pattern (Moiré effect) on the screen (**Fig. 3**). The first flexible digital ureteroscope was introduced in 2007. This scope, the DUR-D (Gyrus ACMI, Southborough, Massachusetts) has been estimated to have an increased image size up to 150% larger than its fiberoptic counterparts.⁴ When compared with the Storz Flex X² (Karl Storz, Tuttlingen, Germany) fiberoptic flexible ureteroscope, it was associated with a faster stone fragmentation rate and corresponding decrease in total operative time.⁵ The next digital scope to be introduced was the Olympus URF-V

(Olympus Corporation, Tokyo, Japan) flexible digital ureteroscope in 2008. When compared with its fiberoptic counterpart, the Olympus URF-P5, it was found to have a higher resolution at a variety of distances and created an image size 5.3 times as large.⁶ Multescu and colleagues⁷ also compared this scope with the Storz Flex X flexible fiberoptic ureteroscope, and they found that the digital scope had more difficulty accessing narrow infundibula 4 mm or less in width. They did, however, find the digital scope to be superior in terms of visibility, maneuverability, and loss of deflection after repeated use. The most recent of the flexible digital ureteroscopes is the Storz Flex-Xc, which is the smallest digital ureteroscope on the market at 8.5F but has not yet been compared with a fiberoptic counterpart. It is not available in the United States at the time of this article; however, it is being used in several European countries.⁸

Although these newer digital scopes are more expensive than their fiberoptic predecessors, proposed improvements in durability may ultimately

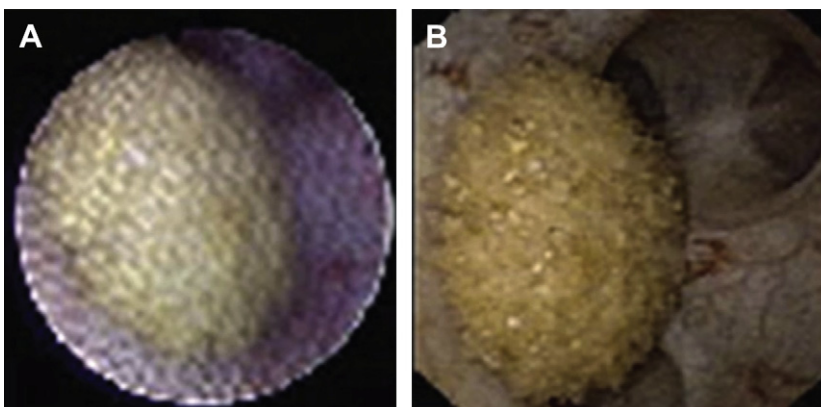


Fig. 3. Comparison of conventional fiberoptic ureteroscopic image⁵⁹ (A) versus digital ureteroscopic image using URF-V (B). (Olympus Corporation, Tokyo, Japan.)

offset differences in price. Knudsen and colleagues⁹ analyzed scope durability among 4 of the most recent fiberoptic flexible ureteroscopes and found a mean range of 5.3 to 18.0 cases until the need for repair. With typical repair costs estimated between \$3000 and \$6000, the need for improved durability cannot be overemphasized.¹⁰ Further comparative studies as well as cost analyses will likely play a large role in the future adoption of these scopes.

SEMIRIGID URETEROSCOPES

Semirigid ureteroscopes (Table 2) have had a slower evolution in terms of technologic improvement relative to flexible ureteroscopes but remain the most commonly used type of scope for access to the upper urinary tract.¹¹ Unlike in flexible ureteroscopy, the transition to digital scopes has been much slower among their semirigid counterparts. One possible reason to explain this slower

Table 2 Currently available semirigid ureteroscope models							
Manufacturer	Model	Digital	Tip Diameter (F)	Proximal Diameter (F)	Number of Channels	Channel Size (F)	Length (cm)
Karl Storz	27001 K/L	No	7.0	13.5	1	5.0	34, 43
Karl Storz	27002 K/L	No	8.0	13.5	1	5.0	34, 43
Karl Storz	27003 K/L	No	9.0	15.0	1	5.0	34, 43
Karl Storz	27010 K/L	No	7.0	9.9	1	3.4	34, 43
Karl Storz	27011 K/L	No	7.0	13.5	1	5.0	34, 43
Karl Storz	27012 K/L	No	8.0	13.5	1	6.0	34, 43
Karl Storz	27014 K/L	No	9.0	15.0	1	5.0	34, 43
Olympus	OES Pro Single	No	6.4	7.8	1	4.2	33, 43
Olympus	OES 4000 Double	No	7.5	7.5	2	3.4 + 2.4	33, 43
Olympus	Pro Video	Yes	8.5	9.9	1	4.2	43
Olympus Gyus ACMI	MR-6A Bagley	Yes	6.9	10.2	2	3.4 + 2.3	33, 41
Olympus Gyus ACMI	MRO-733A	No	7.7	10.8	1	5.4	33
Olympus Gyus ACMI	MRO-742-A	No	7.0	11.2	1	5.4	42
Stryker	SRU-6X	No	6.9	10.0	2	3.4 + 2.5	33, 43
Wolf	8702 (0.517, 0.518)	No	6.0	7.5	1	4.0	33, 43
Wolf	8703 (0.517, 0.518)	No	8.0	9.8	1	5.0	33, 43
Wolf	8708 (0.517, 0.518)	No	6.5	8.5	2	4.2 + 2.55	33, 43
Wolf	8702 (0.523, 0.524)	No	6.0	7.5	1	4.0	31.5, 43.0
Wolf	8703 (0.523, 0.524)	No	8.0	9.8	1	5.0	31.5, 43.0
Wolf	8704 (0.523, 0.524)	No	8.5	11.5	1	6.0	31.5, 43.0
Wolf	8701 (0.533, 0.534)	No	4.5	6.5	1	3.0	31.5, 43.0
Wolf	8702 (0.533, 0.544)	No	6.0	7.5	1	4.0	31.5, 43.0
Wolf	8703 (0.533, 0.534)	No	8.0	9.8	1	5.0	31.5, 43.0
Wolf	8708 (0.533, 0.534)	No	6.5	8.5	2	4.2 + 2.55	31.5, 43.0

adoption is the fact that the rigid shaft design allows for an increased density of fiberoptic bundles, which in turn allows for decreased image degradation¹² Currently there is only one major manufacturer of ureteroscopes that sells a digital semirigid instrument, the Olympus Pro Video scope (also known as the EndoEye ureteroscope). Image properties obtained with a digital scope are favorable. One previous study found that the image size was approximately 2.5 times greater with a digital semirigid scope. One downside, however, is that the current tip diameter is relatively large (8.5F/9.9F) compared with the fiberoptic versions.^{2,13} Multescu and colleagues¹⁴ examined the performance of the Olympus EndoEYE compared with a traditional fiberoptic semirigid ureteroscope and graded visibility and maneuverability on a 5-point scale after each case that it was used. Overall, the digital scope had improved visibility (4.5 vs 3.5) but poorer maneuverability (3.93 vs 4.57) when the patient was not prepped. Furthermore, there was a lower success rate without prepping among the cases where the digital scope was used (84% vs 98%). Decreasing the diameter of the scope is, thus, the logical next step in the evolution of this equipment and will likely be the rate-limiting step before widespread adoption of this technology is seen.

ADVANCED IMAGE SETTINGS

The introduction of high-definition cameras and video has brought visualization capabilities in ureteroscopy to an all-time high; however, there are several other advanced imaging technologies on the horizon. One is the use of narrow band imaging (NBI). NBI, developed by Olympus, is proposed to facilitate the detection of urothelial tumors. This

technology works by enhancing the color contrast of increased vascular patterns caused by angiogenesis in tumor formation. In NBI, two wavelengths of light, 415 nm (blue) and 540 nm (green), are used to illuminate tissue. These wavelengths of light are strongly absorbed by hemoglobin, making tissue with increased vascularity (tumors) appear dark relative to surrounding normal mucosa (Fig. 4).¹⁵ Currently, the only ureteroscope to offer such capabilities is the Olympus URF-V. To date, only one published study has investigated the clinical utility of using NBI in the diagnosis of upper tract urothelial carcinoma, though results were promising with an improved tumor detection relative to white light imaging by approximately 23%.¹⁶

Another advancement to expect in the next several years is the application of 3-dimensional technology. The use of 3-dimensional vision has been shown to enhance surgeon performance in laparoscopic and robotic settings,¹⁷ and the application to endoscopy would be a logical next step.

Virtual endoscopy is yet another technology that is currently being developed. The idea for this is that the combination of ureteroscopy and computer-engineered software might help construct a reliable, 3-dimensional image of the ureteral anatomy. This technology might help identify tumors and could play a useful role in the surveillance of upper tract urothelial carcinomas; however, this technology is currently in its early infancy.^{18,19}

Finally, in 2011, a pilot study was performed demonstrating the use and efficacy of robotic flexible ureteroscopy. This platform was converted from a robotic console designed for intracardiac applications but modified for use in ureteroscopy (Fig. 5). Eighteen patients were successfully treated with this method. Benefits mentioned by

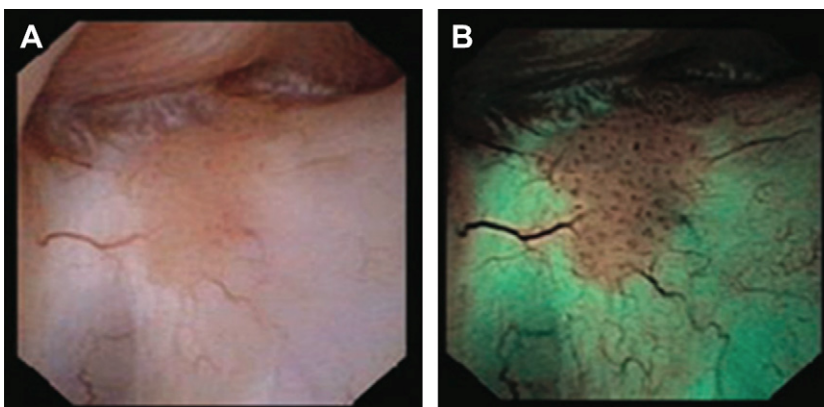


Fig. 4. Appearance of upper tract urothelial tumor during digital ureteroscopy using conventional white light (A) and Narrow-Band Imaging (B). (From Traxer O, Geavlete B, de Medina SG, et al. Narrowband imaging digital flexible ureteroscopy in detection of upper urinary tract transitional-cell carcinoma: initial experience. J Endourol 2011;25(1):19-23; with permission.)



Fig. 5. Robotic flexible ureteroscopy.²⁰

the investigators included the ergonomic advantage of being seated and using the robotic console as well as the ability to scale and fine tune motion to a very small degree based on stone fragment size. Disadvantages included the large size of the robotic sheath (14F), which required prestening in all cases, and the procedure being quite cumbersome in its infancy.²⁰ Time will tell whether there is a role and benefit to this technique.

LITHOTRIPSY DEVICES

Numerous lithotriptors have been previously used for the purpose of stone fragmentation, including electrohydraulic (EHL), pneumatic, and ultrasonic. Lasers, however, are by far and away the most commonly used intracorporeal lithotripsy devices. Their use for this purpose was initially described in 1987²¹; and in the time since, they have revolutionized endourology. Currently, the holmium:yttrium-aluminum-garnet (Ho:YAG) laser is the most commonly used laser for lithotripsy²² because of its superior complication and stone-free rates compared with pneumatic²³ and EHL²⁴ lithotriptors. The Ho:YAG laser works via the creation of laser pulse energy, which is absorbed by the targeted structure causing destruction.²⁵ The advantages of the Ho:YAG laser over other lasers are its ability to fragment stones of essentially all compositions²⁶ with minimal retropulsion²⁷ and surrounding tissue damage. It has been estimated that the absorption depth of this laser is as low as 0.4 mm.²² Additionally, it has been shown to achieve smaller stone fragments than other lasers or lithotripsy devices, maximizing the likelihood of stone passage.²⁸

It is likely that in the coming years there will be new lasers available on the market. The most likely candidates are the erbium:YAG (Er:YAG) fiber and the thulium laser fiber.²⁹ The potential benefit of the Er:YAG laser is a higher high-temperature water absorption coefficient, which has been shown to correspond with a 2 to 3 times increased

stone fragmentation efficiency *in vitro*.³⁰ However, this laser requires a less flexible, more expensive midinfrared fiber that has limited its clinical applicability compared with the silica fibers used with the Ho:YAG laser.²⁹ Another laser that has been investigated for use in lithotripsy is the thulium laser, which also has a higher high-temperature water absorption coefficient and has been found to achieve stone vaporization rates 5 to 10 times higher than the Ho:YAG laser.³¹ Additional clinical trials using these novel lasers for the purpose of lithotripsy will be necessary before determining their clinical utility. For the time being, they are not available in the United States.

One of the few challenges when using a Ho:YAG laser is that the size of the laser can decrease the scope flexion. The 365- μ m laser fibers have been estimated to lead to a loss of 24° to 45°, whereas the 200- μ m laser fiber has been estimated to lead to a loss of 9° to 19°.^{32,33} Several companies manufacture a 150- μ m laser fiber, which has been shown to be the most flexible of the currently available laser fibers³⁴; and it is possible that even smaller laser fibers will be created. The authors recommend using a 365- μ m-type fiber when using a rigid ureteroscope and a 200- μ m-type or smaller fiber when using a flexible ureteroscope. The 200- μ m fiber allows better deflection, thereby allowing better access to the upper urinary tract. It also likely leads to better durability of the scope by decreasing stress on the deflection mechanisms. However, the 200- μ m fiber can have more burn back (or degradation) of the fiber, especially when treating a harder and/or larger stone burden. The larger fibers work well in the rigid ureteroscopes because the working channels are also more capacious, which allows better irrigation flow.

Another potential limitation in using lasers is the potential for scope damage with the introduction of the laser fiber or accidental activation of the fiber when it is still within the scope. Durak and colleagues³⁵ evaluated the utility of a protective laser sheath called the Flexguard (Lisa Laser Products, Katlenburg-Lindau, Germany), which they found was able to decrease the amount of force necessary to insert the fiber through the working channel. However, it was unable to protect the scope from laser damage and additionally led to a loss in deflection capability and irrigant flow rate. One subsequent study, however, demonstrated that this device reduced mechanical damage to the flexible ureteroscope after approximately 40 to 50 uses.³⁶

Another device meant to address the potential for laser damage to the ureteroscope is the endoscope protection system (EPS) (Gyrus ACMI,

Southborough, Massachusetts) available with the DUR-D flexible ureteroscope. The EPS works by immediately terminating holmium laser energy when it is drawn back into the ureteroscope. In vitro, it was shown to successfully shut down the laser 120 out of 120 times with retraction.³⁷ In 20 cases whereby the EPS was used in vivo, the system shut down the laser in 50% of the cases when the laser was still safely outside the scope, likely from stone fragments or dust interfering with detection capability. However, the EPS was successful in shutting down the laser in all 80 attempts made at different speeds to retract the active laser into the scope.³⁸

Another method of protecting the inner channel of the flexible ureteroscope and laser fiber tip is by only advancing the laser through the tip of the scope when the scope is not deflected (at the zero degree position). Acknowledging the potential for scope damage when a laser is inserted through a deflected scope tip, Boston Scientific (Natick, Massachusetts) has recently released the TracTip fiber, which is a 200- μ m fiber with a ball tip that allows the fiber to be advanced while the scope is deflected because the ball tip can likely protect damage to the inner channel.

Finally, although lasers have recently dominated the market, pneumatic lithotripters may be making a return. The LMA StoneBreaker (Cook Inc, Bloomington, Indiana) is a high-powered single-pulse pneumatic lithotripter that causes stone fragmentation via direct contact. It is powered by carbon dioxide gas cartridges. Nerli and colleagues³⁹ used it to treat ureteral stones in 110 cases and found a mean number of only 8 shocks necessary to fully fragment the stone into sizes suitable for clearance. There were no complications or subjective ureteral trauma in any case. Benefits of this device are the fact that it is reusable and relatively inexpensive, with an estimated cost of less than \$5 per carbon dioxide cartridge. It was recently compared with the Ho:YAG laser for use with rigid ureteroscopy for distal ureteral stones in a randomized controlled study, with no differences seen for operative time, complication rate, or stone-free rate.⁴⁰

ACCESSORY INSTRUMENTS

Guidewires

A wide variety of accessory instruments have been introduced over the past several years with the intent of improving the ease and ability to treat stones. Guidewires remain critical in gaining access to the upper tracts. Although several different guidewires exist commercially, each has its unique advantages. Clayman and colleagues⁴¹

found that the Glidewire (Boston Scientific) is the safest owing to increased flexibility and a tendency to bend when a point of obstruction is encountered. They also demonstrated that the Amplatz super stiff wires (Boston Scientific, Applied Medical [Rancho Santa Margarita, California]) were the most resistant to bending and were the best choice for passing instruments.

The current trend in guidewires has been the introduction and widespread adoption of the hybrid guidewire. These wires offer the advantage of hydrophilic distal tips ideal for bypassing obstructing stones as well as a stiff body optimized to maintain rigidity and to allow for the passage of instruments.³ A recent comparison of 2 commonly used hybrid wires, the U-Nite (Bard Medical, Covington, Georgia) and Sensor (Boston Scientific), found that the Sensor wire had a greater friction force, potentially indicating it as a better choice for use as a safety wire because of its decreased likelihood of accidentally being pulled out. The Sensor wire was also found to have a more flexible tip, potentially indicating that it would be a better choice to maneuver around obstructing stones. The U-Nite, on the other hand, was found to have a rounder tip under electron microscopy, potentially meaning it is less likely to cause urothelial injury, such as submucosal tunneling.⁴²

URETERAL ACCESS SHEATHS

The last several years have also brought about several conceptual changes in terms of access sheaths. Although conventional wisdom used to be that the larger the access sheath, the greater the flow, a recent study by Ng and colleagues⁴³ found minimal differences between a variety of different-sized access sheaths (10F to 16F) when the working channel was occupied. The same group introduced 2 novel configurations that did improve flow dynamics. In one configuration, they used a 4F ureteral access catheter solely for irrigation inflow adjacent to a 10F access sheath; in the other, they used a 5F ureteral access catheter within a 16F sheath. They found that these two configurations created the highest flow rates. Meanwhile, the potential for ureteral injury when an access sheath is used may be higher than previously thought. Traxer and colleagues⁴⁴ recently evaluated 136 patients who had ureteral access sheaths used during retrograde intrarenal stenting. They found some degree of ureteral wall injury estimated in approximately 50% of all cases, though these numbers were significantly lower among patients who were prestenated, raising consideration that a routine ureteral access sheath may not be ideal.

STONE RETRIEVAL DEVICES

In terms of stone retrieval devices, nitinol baskets have essentially replaced stainless steel baskets completely owing to improved memory and increased flexibility with less resulting loss of scope deflection.⁴⁵ Today there are a wide variety of commercially available nitinol stone baskets (**Table 3**). The most recent generations of baskets are available in small sizes, often less than 1.5F, with the goal of preserving maximum irrigation during procedures. Korman and colleagues compared 3 of the smaller baskets on the market, including the Boston Scientific Optiflex (1.3F), Cook N-Circle (Cook Inc, Bloomington, IN) (1.5F), and Sacred Heart Medical Halo (1.5F) (Sacred Heart Medical Inc, Minnetonka, Minnesota) in a series of studies. Of the 3, they found the Sacred Heart basket to have the greatest radial dilating force and led to the fastest stone extraction times when tested in a ureteral model.^{46,47} The Optiflex was associated with significantly slower extraction times. Magheli and colleagues⁴⁸ later compared the same 3 baskets; in this case, they found that the 1.3F Optiflex led to a significantly decreased loss of deflection and increased flow rate relative to the two other 1.5F devices.

Aside from smaller sizes, there have been several other unique basket designs recently introduced. The Escape basket (Boston Scientific) allows for simultaneous laser lithotripsy with a 200- μ m holmium laser fiber via an inner channel within the basket wiring while the stone is held in the basket. Although this basket has been demonstrated to be both safe and effective *in vivo*,⁴⁹ there are currently no published studies comparing its use with other available stone baskets. Another is the N-Gage basket (Cook Inc, Bloomington, IN) whose design combines the entrapment capabilities of traditional baskets with the superior release capabilities of pronged graspers. The improved ability to easily release the stone helps optimize the surgeon's ability to reposition the stones into the upper pole where laser is potentially more efficacious. Simultaneously, this basket's improved catch-and-release properties decrease the likelihood of stones becoming trapped in the device, thereby potentially preventing ureteral injury.

One of the remaining problems with retrieval baskets in general is that the number of times they need to be used in a single case to achieve true stone-free status can be cumbersome. To address this, Tan and colleagues⁵⁰ recently investigated a method of magnetizing calcium stone particles using paramagnetic microparticles with the intention of attracting smaller fragments to a magnetic instrument. They then invented an 8F

magnetic tool able to be back loaded through a standard flexible ureteroscope to the collecting system. Although there was no significant difference compared with using a nitinol stone basket, they did retrieve more small stones (1.5–2.0 mm in size) using the magnetic device.

ANTIRETROPULSION DEVICES

Antiretropulsion devices are another novel type of accessory instrument gaining popularity in the world of ureteroscopy. Proximal stone migration remains a bothersome occurrence in many lithotripsy cases; therefore, a variety of ureteral occlusion and antiretropulsion devices have been created (**Fig. 6**). Three of the studied devices include the Stone Cone (Boston Scientific), Accordion (Percutaneous Systems Inc, Palo Alto, California), and NTrap (Cook Inc, Bloomington, IN). The Stone Cone was the first to become commercially available. It consists of a nitinol wire coiled in the shape of a cone that is covered in a 3F polytetrafluoroethylene cover that can be inserted distal to the area of a stone and prevent proximal migration. It has previously been demonstrated to be both safe and effective. Eisner and Dretler⁵¹ studied its use in 133 cases of ureteroscopy for ureteral stones and found evidence of only 2 retro-pulsed fragments greater than 2 mm in size. It has also been estimated to have a 20% increase in the stone-free rate compared with controls. The NTrap was the second antiretropulsion device made commercially available. It is a deployable wire mesh net created of tightly wound nitinol wires. A recent meta-analysis found that cases in which the NTrap device was used had threefold higher stone-free rates as well as a decreased need for auxiliary shockwave lithotripsy procedures than controls.⁵² More recently, the Accordion device has been introduced. This device is comprised of a flexible polyurethane film that, when deployed, conforms to the ureter to prevent stone retropulsion. *In vitro* studies have demonstrated an excellent ability to prevent retropulsion as well as associated improvement in terms of fragmentation rate with its use.⁵³ Additionally, there is a suggestion that it may be a more durable device owing to the improved ability to withstand laser damage.⁵⁴ A recent *in vivo* study demonstrated improved fragmentation efficiency and stone clearance with a significant reduction in retrograde migration during fragmentation.⁵⁵ All 3 of these devices have the issue that the scope needs to be placed beside the device; therefore, they could be difficult to use in cases with a baseline narrow distal ureter.

Table 3
List and features of current nitinol stone retrieval baskets

Manufacturer	Model	Available Sizes (F)	Available Basket Sizes (mm)	Available Lengths (cm)	Features
Bard	Dimension	2.4, 3.0	10, 13, 16	115	Articulating basket, 4-wire design, zero tip
Bard	Expand212	3.0	11	90, 115	Articulating basket, 2-1-2-1 wire design, filiform tip
Boston Scientific	Escape	1.9	11, 15	90, 120	4-wire cage, 2-port adapter allows simultaneous use of 200- μ m laser fiber
Boston Scientific	Optiflex	1.3	6, 7, 9, 11	90, 120	Able to articulate and rotate 360°, small size preserves irrigation and deflection
Boston Scientific	Zerotip	1.9, 2.4, 3.0	12, 16	90, 120	Zero tip allows atraumatic use adjacent to parenchyma
Cook	NCircle	2.4	10, 20	115	Triangular shape allows very large wire mass, tipless design
Cook	NForce	2.2, 3.2	—	115	3-wire basket with maximal radial dilating ability suited for ureteral opening
Cook	NGage	1.7, 2.2	8, 11	115	Suited for optimal engage and release to allow repositioning
Sacred Heart (Minnetonka, Minnesota)	Halo	1.5	12	90, 120	Tipless, small size maximizes deflection and flow
Sacred Heart	Vantage	2.4, 3.0	16	90, 120	
Sacred Heart	Paragon	2.4, 3.0	10	90, 120	2 single and 2 paired wire design optimizes radial force, ideal for ureteral stone capture
Sacred Heart	Apex	2.4	15	90, 120	Zero tip for atraumatic use

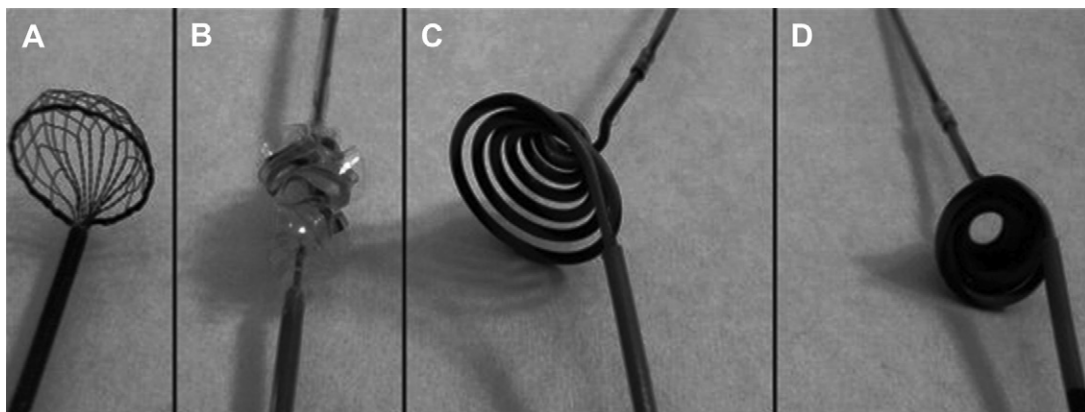


Fig. 6. Currently available antiretropulsion devices. (A) N-trap (Cook Inc, Bloomington, IN), (B) Accordion (Percutaneous Systems Inc, Palo Alto, CA), (C & D) Stone Cone 10 mm and 7 mm (Boston Scientific, Natick, MA).⁵⁷

There are only a few studies available that have compared these devices with each other. Both the NTrap and Stone Cone were shown to have excellent ability of blocking proximal migration of fragments as small as 1.5 mm in a porcine model, although the NTrap was found to be capable of blocking even smaller fragments.⁵⁶ Ahmed and colleagues⁵⁷ compared the different physical characteristics of each device. Most importantly, the 3 devices seemed to be comparable and equally effective in terms of preventing stone migration. However, they did find that the Stone Cone required the most attempts and force to deploy, whereas the Accordion took the most time. The NTrap was found to have the greatest tip stiffness, potentially increasing the likelihood of ureteral injury; however, this difference was not statistically significant.

Two new devices have recently been introduced with unique features distinguishing them from the other available antiretropulsion devices currently on the market. The XenX (Xenolith Medical LTD, Kiryat-Gal, Israel) serves the dual purpose of both an occlusion device as well as a guidewire through which the surgeon is able to place a stent at the end of the procedure. Although this device is not yet commercially available, early results have been promising. Sarkissian and colleagues⁵⁴ tested this device in a porcine model and found it to be comparable in terms of ease of passage to the NTrap and Stone Cone. They also found that the XenX was superior in terms of preventing stone migration in vitro. The other new device currently being marketed is Backstop (Boston Scientific). Backstop is a reverse thermosensitive water-soluble polymer that allows temporary occlusion of the desired segment of ureter. The polymer is applied using a small ureteral access catheter and can then be flushed away with

irrigation of cold saline. The proposed benefit of Backstop is the fact that it does not require leaving a mechanical element in the ureter while operating that can potentially interfere with the procedure. To date, there has been only one published study analyzing outcomes of its use. Rane and colleagues⁵⁸ prospectively randomized 68 patients with solitary ureteral stones to either ureteroscopy or lithotripsy with or without Backstop. They found a statistically significant decrease rate of retropulsion in the Backstop group (8.8% vs 52.9%), with no adverse events in this group.

SUMMARY

Ureteroscopic technology continues to improve at a rapid pace. Recent advancements in both imaging equipment and instrumentation have not only improved the operator's ability to treat stone disease but have also led to improved outcomes. It is likely that the continued evolution of such technologies will continue to push the conventional limits of a retrograde treatment approach to the upper urinary tract.

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Management of Stones in Abnormal Situations

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KEYWORDS

- Nephrolithiasis • Pregnancy • Horseshoe kidney • Urinary diversions • Calyceal diverticulum
- Pelvic kidneys • Transplant kidneys • Autosomal dominant polycystic kidney disease

KEY POINTS

- The management of urinary calculi in abnormal situations continues to pose challenges to urologists. Abnormal situations include pregnancy, aberrant anatomy, kidney transplants, calyceal diverticuli, urinary diversions and autosomal dominant polycystic kidney disease.
- A combination of aberrant anatomy, urinary tract infections, and metabolic changes predispose these patients to an increased incidence of stone formation.
- Metabolic evaluation and medical therapy are arguably more important in these patients, as metabolic abnormalities can be rather common.

INTRODUCTION

The management of urinary calculi in abnormal situations continues to pose challenges to urologists. Abnormal situations include pregnancy, aberrant anatomy, kidney transplants, calyceal diverticuli, urinary diversions, and autosomal dominant polycystic kidney disease (ADPKD). A combination of aberrant anatomy, urinary tract infections, and metabolic changes predispose these patients to an increased incidence of stone formation. The aims of treatment are similar to normal situations. That is an attempt at complete clearance of all stone fragments with the least invasive means possible while trying to minimize secondary procedures and complications. Unfortunately, the aberrant anatomy makes access and clearance of these calculi more difficult to accomplish.

Metabolic evaluation and medical therapy are arguably more important in these patients, as metabolic abnormalities can be rather common, as will be discussed later. These changes often lead to progression of remnant stones requiring secondary treatments and increasing morbidity to the patient.

The options for treatment include open procedures, extracorporeal shockwave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL), laparoscopy, and ureteroscopy. The choice of procedure must take into account difficulties with access and the anatomic configuration of the kidney and stone. In general, our experience is that most if not all urinary calculi can be managed by minimally invasive procedures, obviating the need of open procedures, although we do acknowledge that in the situations of a lack of access to equipment or inexperience, open procedures may be the safer option with better stone-free rates.

HORSESHOE KIDNEYS

Horseshoe kidneys are the most common renal malformation with an incidence of 1 in 400 births. There is also a preponderance toward males with a 2:1 ratio.¹ As the renal units ascend during fetal development there is abnormal fusion of the mesonephric blastemas. This leads to incomplete ascension and also malrotation of the kidneys. The final product is a fused kidney in the shape of

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a horseshoe that is limited by the inferior mesenteric artery and lies more caudally (**Fig. 1**). The kidney calyces tend to be posterior and medial and the upper pole calyces lie more cranial and lateral (**Fig. 2**).² The ureters have a high insertion and deviate more anteriorly, as they have to cross the renal isthmus (**Fig. 3**). This high insertion and crossing of the renal isthmus may lead to increased incidence of urinary stasis.

Horseshoe kidneys are associated with up to 100% incidence of urinary metabolic abnormalities, 40% recurrent urinary tract infections, and 35% incidence of suboptimal urinary outflow.³ There is a 20% median incidence of stones in horseshoe kidneys¹ with most in the posterior lower pole calyx and the renal pelvis. Most of these stones are calcium oxalate.

As the innervation of the horseshoe kidney is the same as that of the normal kidney, symptoms of renal colic are similar; however, atypical presentations of vague abdominal pain or emesis may occur owing to the different lie of the kidneys.

The decision of treatment option will have to take into consideration aberrations in anatomy that may include aberrant vasculature, distortions of the renal collecting system, and interposing bowel between skin and kidney. The presence of uretero-pelvic junction (UPJ) obstruction should also be determined before treatment, as it will affect outcomes of certain procedures. The options for treatment include ESWL, ureteroscopy, PCNL, laparoscopy, and open surgery.

ESWL

ESWL is the least invasive modality of treatment for horseshoe kidney stones. There are a number of factors that may make shockwave therapy less efficacious. The horseshoe kidney sits lower

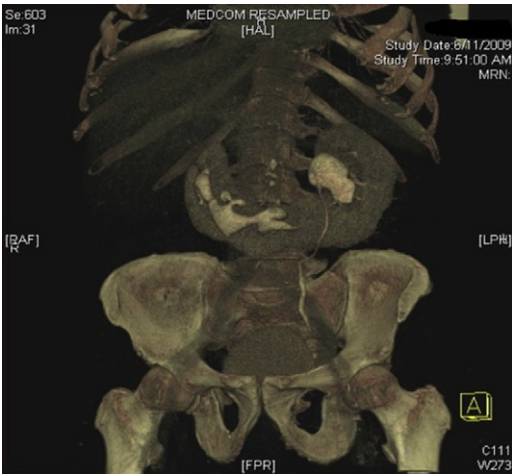


Fig. 1. Horseshoe kidney.



Fig. 2. Horseshoe kidney with stone. Note the access angle is 15° as opposed to the 30° for normal kidneys.

in the abdominal cavity and tends to be more medial. The end result of these changes is that vertebral bodies, transverse processes, bony pelvis, and bowel gas shadows may obscure targeting of the stone. Furthermore, if the stone lies below the pelvic brim, a prone ESWL will have to be attempted and this has a higher chance of traumatizing the overlying bowel.

The second problem is the high insertion and kinking of the ureter as it crosses the renal isthmus. Contrast studies and excretory studies may also need to be done to exclude UPJ obstruction in these kidneys. The net effect is that even if the stones are fragmented, there is poor passage of fragments.

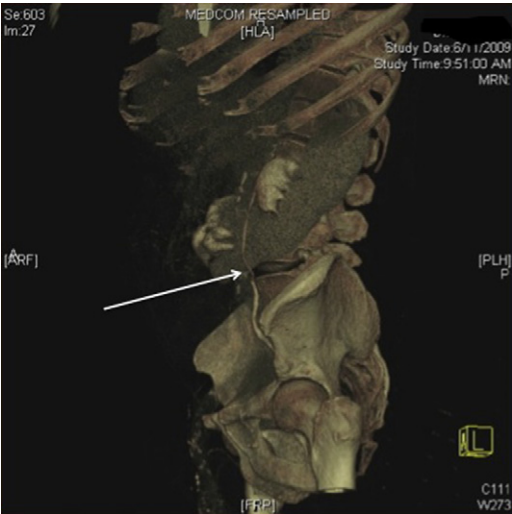


Fig. 3. Anterior deviating ureter with kink over the isthmus.

There have been a number of studies looking at the efficacy of shockwaves for stones in horseshoe kidneys and the success rates range from 28% to 80%.⁴⁻⁶ Many of these stones required multiple sessions of shockwave and even the definitions of success are debatable, as remnant stone fragments smaller than 4 mm were considered as successful treatments in some of these articles.

Size of stones treated influences the success of ESWL in these patients. Sheir and colleagues⁷ documented a success rate of 79% for stones smaller than 15 mm, which dropped to 53% once stones were larger than 15 mm. **Table 1** shows the results of studies attempting to clear stones in horseshoe kidneys with ESWL. Clayman⁸ suggested that percutaneous treatment maybe more appropriate for stones larger than 10 to 15 mm.

In one of the largest studies to date, Ray and colleagues⁹ treated 41 horseshoe kidneys with stones with ESWL. They managed single treatment success of 25% and stone free rate of 9.1%. Overall success was 63.6% with stone-free rate of 39.1%; 73.0% of the patients needed auxiliary treatments that included repeat ESWL, percutaneous nephrolithotomy, or ureterorenoscopy.

The consensus is that ESWL should be reserved for stones smaller than 20 mm, in nondependent locations of the renal pelvis with minimal renal collecting system dilation. UPJ obstruction should also be excluded before proceeding. If the patient is not stone free after ESWL, ureteroscopy or percutaneous clearance of stones should be considered.

Ureteroscopy

The aberrant anatomy of horseshoe kidneys with anterior, tortuous, and high insertions of the ureters make semirigid ureteroscopic treatment

of the upper ureteric or renal calculi challenging in the best of circumstances. With the advent of flexible ureteroscopes and lasers there have been a number of small series that have explored the use of ureteroscopy for the management of renal calculi in horseshoe kidneys. Andreoni and colleagues¹⁰ in a case report described the use of an access sheath and flexible ureteroscope to clear 3 stones, the largest being 12 mm, leaving no fragments larger than 2 mm. In a later series, Weizer and colleagues¹¹ treated 4 patients with stones in a horseshoe kidney with a flexible ureteroscope. The average size was 1.4 cm, with a mean operative time of 126 minutes and a success rate of 75%. The largest series by Mollmard and colleagues¹² consisted of 17 patients; 70% of the patients were treated with flexible ureteroscopy after failure with either PCNL or ESWL. Average stone burden was 16 mm and average operative time was 106 minutes; 41% required staged procedures. They were able to achieve a stone-free rate of 88.2% as defined by no remnant stones larger than 3 mm. Ureteroscopic management continues to be challenging. Its indication is limited to stones smaller than 2 cm. Access sheaths and ureteric dilators are often required and patients who choose this modality must be prepared for staged procedures.

PCNL

Ever since the publications by Wickham and Kellett¹³ and Clayman and colleagues,¹⁴ percutaneous nephrolithotomy has become the standard of care for stones larger than 2 cm or for cases that have failed ESWL.¹⁵ An understanding of anatomy is critical for the urologist who desires to attempt PCNL. The horseshoe kidney lies lower and is malrotated such that the posterior calyx lies in an anterior-posterior plane with the renal pelvis lying anteriorly. The upper pole calyx lies

Table 1
Results of SWL patients with horseshoe kidneys

Investigator, Y	Mean Stone Diameter, mm	No. of Patients	Fragmentation Rate, %	Stone-Free Rate, %	Retreatment Rate, %
Esuvaranathan, ¹²² 1991	12	7	Not Reported	59	50
Kirkali et al, ⁵ 1996	24	18	78	28	57
Smith, ¹²³ 1989	Not Reported	14	Not Reported	79	29
Bhatia and Biyani, ² 1994	28	27	Not Reported	70	48
Sheir et al, ⁷ 2003	13.5	49	Not Reported	71	71
Tunc et al, ⁶ 2004	22	46	Not Reported	66	Not Reported
Ray et al, ⁹ 2011	9.5	41	Not Reported	39.1	71

posterior-lateral and sits lower than in the normal kidney. Other associated abnormalities include a higher incidence of UPJ obstruction (15%–33%)¹⁶ and aberrant vasculature as the vessels enter the isthmus dorsally, precluding percutaneous access there.¹⁷ Another consideration is the possibility of a retrorenal colon, which would affect access (**Fig. 4**). A computed tomography (CT) scan with contrast and possibly functional nuclear medicine studies are important to look for these abnormalities.

Access is best achieved via the upper pole posterior calyx. This access gives direct access toward the renal pelvis and is associated with a low risk of pneumothorax, as the upper pole lies well below the costophrenic angles of the lung.¹⁸ As the horseshoe kidney lies more anteriorly, the access tract tends to be longer. This is especially so for obese patients. The horseshoe kidney, by virtue of its position, is more fixed and excessive torque on the kidney can lead to bleeding.¹⁹ A full complement of baskets and flexible nephroscopes should be available for the successful clearance of stones.

The aim of PCNL should be complete stone-free status. This is especially so as the high ureteric insertion leads to stasis and even small residual fragments may have difficulty passing and may in time act as a nidus for stone formation. Success rates in PCNL range from 65.5% to 75.0%.^{1,20} These numbers are contentious, as in many of the articles there is no consistent definition of stone-free status.

Complications are similar to PCNL in a normal kidney. These include urinary tract infection (UTI), hematuria, renal hematomas, urine leak, and

obstruction, although, as previously mentioned, risks of pneumothorax and hydrothorax with an upper pole access is much lower because the kidney is low lying.¹⁸

Laparoscopy

This is a rarely used modality of treatment for stones in horseshoe kidneys. The anterior location of the kidney and its renal pelvis suggests that access to the stones via a laparoscopic pyelolithotomy should be easier. Another added advantage of a laparoscopic approach would be the ability to treat a UPJ obstruction with a laparoscopic pyeloplasty. Nambirajan and colleagues²¹ described a successful bilateral laparoscopic pyelolithotomy and more recently Symons and colleagues²² described the laparoscopic management of a large staghorn stone. Surgical time was 3 hours and the patient was discharged without complications.

In conclusion, for stones smaller than 2 cm in nondependent locations, ESWL is a viable option for treatment. PCNL should be reserved for stones larger than 2 cm or after ESWL failure. Ureterscopy and laparoscopy are alternatives that show promise, although the experience in the literature is limited. In the setting of UPJ obstruction secondary to a crossing vessel, laparoscopy would be the treatment of choice, as it allows concomitant treatment of the obstruction.

PELVIC KIDNEY

The pelvic kidney occurs owing to a failure of ascent of the kidney during development. Its incidence is estimated at 1:2200 to 1:3000. Pelvic kidneys have a significant portion of the kidney below the pelvic brim (**Fig. 5**). They are malrotated and have high insertion of the ureter, which may predispose them to urinary stasis and calculi formation.²³ There is also an increased incidence of UPJ obstruction. This low position in the pelvis, associated with other abnormalities, provides unique challenges to management of urolithiasis in these kidneys.

Like the horseshoe kidney, innervation of the kidney follows that of the normally positioned kidney and symptoms are typical as for a kidney in the normal position.

ESWL

As part of the workup for ESWL for calculi in the pelvic kidney, it is important to exclude UPJ obstruction, as this would have consequences on stone fragment passage after ESWL. Because of the low-riding position of the pelvic kidney, the

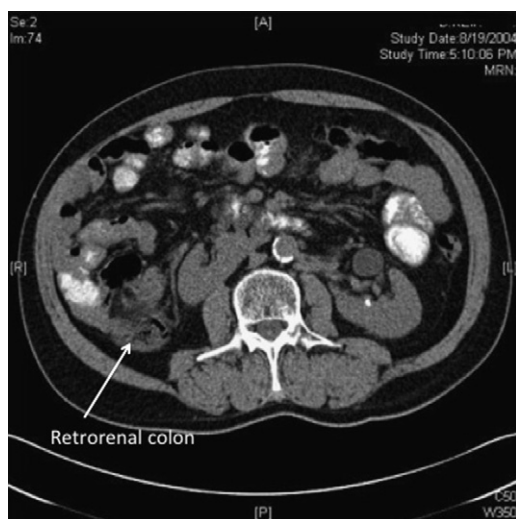


Fig. 4. Retrorenal colon.



Fig. 5. Right pelvic kidney with stones: note it lies below the pelvic brim.

patient often has to have treatment in the prone position, as the bony pelvis would get in the way of the ESWL shockwaves. Loops of bowel anterior to the pelvic kidney can also reduce the efficacy of the shockwaves.

Data for ESWL treatment of stones in pelvic kidneys is limited to small case series. Stone-free outcomes range from 25% to 92%.^{24–26} The numbers are contentious, as there are different definitions of stone-free status. For example, Talic²⁷ treated 14 patients with a mean stone size of 2.35 cm² with an absolute stone-free status of 57.2%, and 35.7% of patients had remnant stones smaller than 4 mm. The more successful studies tried to exclude obstruction at the UPJ and oftentimes the patients underwent multiple procedures for stone clearance. Overall, there is relatively good stone clearance if there is no concomitant obstruction.

Ureteroscopy

There are a few reports of ureteroscopic management of pelvic kidney stones. Weizer and colleagues¹¹ treated 4 patients with pelvic kidney urolithiasis with flexible ureteroscopy. The mean stone size was 14 mm with a stone-free rate of 75%. Mean operative time was 126 minutes. This is comparable to success rates with ESWL without the need for secondary procedures. These investigators encouraged the use of access sheaths to help straighten the ureter. The access sheaths also allowed for rapid access to the upper ureter but its use must be cautioned, as these tortuous, anterior ureters have a risk of trauma from passage of the access sheaths. An effort should be made to

achieve stone-free status, as the ureters usually have a high insertion and remnant stones have poor potential to pass spontaneously.

PCNL

Unlike horseshoe kidneys, the location of the kidney within the pelvis makes PCNL challenging. The PCNL will need to be performed in the supine position and requires a transperitoneal approach. As can be imagined, this approach has the potential for significant injury to intra-abdominal contents, in particular the bowel. There is also the problem of urine leak, which if it occurs is not limited to the retroperitoneum, as is in the case with a retroperitoneal PCNL.

Desai and Jasani²⁸ reported on the use of ultrasound-guided supine transperitoneal PCNL. In brief, the ultrasound is used for both calyceal localization and also as a tool to push away bowel to reduce the risk of bowel injury during the access. They achieved a 100% stone-free status in 16 patients with 1 case of bowel injury that was managed conservatively.

Watterson and colleagues²⁹ reported a posterior approach via the sciatic foramen; unfortunately, this approach was associated with postoperative femoral neuropathy.

Others have tried a laparoscopic-assisted trans-abdominal percutaneous approach to the kidney. Eshghi and colleagues³⁰ reported the first such procedure in 1985. The patient is positioned in a Trendelenburg position and 3 to 4 ports are inserted. A ureteral catheter is placed so that percutaneous access can be directed both visually and fluoroscopically. Once puncture of the kidney is successful, it is dilated as per usual PCNL. It should be noted that the distances that need to be traversed are longer and long instruments may be needed.

There have been variations on this combined laparoscopic/percutaneous nephrolithotomy technique. Zafar and Lingeman³¹ described the laparoscopic suturing of the nephrotomy so that percutaneous drainage is not required. A total extraperitoneal approach was described by Holman and Toth.³² A space maker balloon was inserted into the extraperitoneal space and the percutaneous access was directed both visually and fluoroscopically. An advantage of this last variation is that if there is a leak, it is into the extraperitoneal space.

Laparoscopy

In pure laparoscopic pyelolithotomy, ports are placed transperitoneally in a patient who is in the Trendelenburg position.³³ Bowel is displaced and a pyelotomy is made sharply. Stones are then

extracted laparoscopically with graspers under direct vision. Flexible nephroscopes can then be passed into the collecting system and stones can then be extracted by basket. A double J stent is usually recommended, as leakage into the peritoneal cavity can have serious consequences. Ramakumar and Segura³⁴ achieved 90% and 80% stone free rates at 3 months and 12 months respectively in 19 patients using this approach.

Laparoscopy also allows simultaneous management of a UPJ obstruction. The pyelotomy can be extended distally as a fengerplasty or a formal dismembered pyeloplasty can be performed.

There have been a series of cases in which retroperitoneoscopy was performed. The space was created by a balloon but it was noted in some instances that there was difficulty creating the space.³⁵ When the renal pelvis was accessed successfully the success rate was 83%.

In the age of robotic surgery, a number of cases of robot-assisted laparoscopic pyelolithotomy have been performed. The advantages of the robot relate to improved optics and also easier closure of the pyelotomy. This is especially advantageous in the patient who undergoes concomitant pyeloplasty. The stone-free rates approach 80% to 100%.^{36,37}

Our opinion is that ESWL or ureteroscopy is a possible first treatment option for stones smaller than 2 cm if UPJ obstruction has been excluded. In the presence of stones larger than 2 cm or if UPJ obstruction is present, laparoscopy or PCNL may be a better option as first-line therapy.

CALYCEAL DIVERTICULAR STONES

Calyceal diverticula are nonsecretory, transitional cell epithelium-lined cystic cavities within the renal parenchyma with an incidence of less than 1% (Fig. 6).³⁸ They may have narrow infundibuli that may predispose them to recurrent infections, pain, and stone formation. The incidence of stone formation is between 10% and 50%.^{39,40}

Most stones are calcium oxalate or mixed stones; in a urine metabolic evaluation of patients with diverticular calculi by Auge and colleagues,⁴¹ it was found that all patients with diverticular calculi had metabolic abnormalities.

Indications for treatment include, pain, recurrent infections, hematuria, and progressive stone growth.⁴²

ESWL

When ESWL is chosen as the primary treatment modality, stone-free rates are low, ranging from 20% to 58%.^{43–45} Streem and Yost,⁴³ who had one of the higher success rates when treating

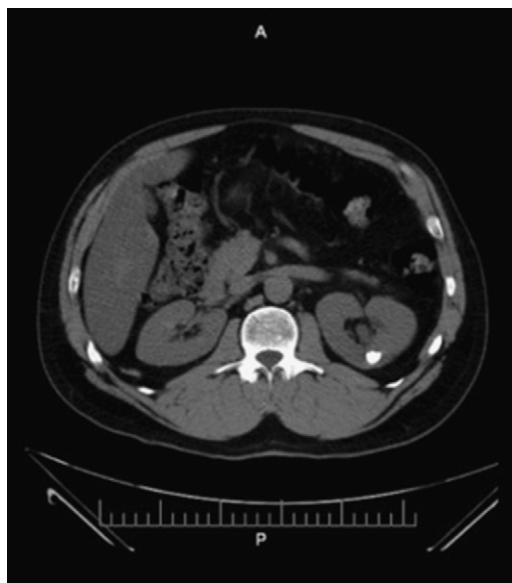


Fig. 6. Left calyceal diverticulum stone.

calyceal diverticular stones, suggest that patient selection plays an important role in treatment success. In their study, 21 renal units were treated with ESWL. Inclusion criteria for treatment was stones smaller than 1.5 cm in calyceal diverticuli with a wide and short infundibulum. They achieved a 58% stone-free rate with 1 treatment.

Surprisingly, even with dismal stone-free rates, pain-free rates after ESWL are much higher, ranging from 65% to 75%.^{44,45} There are a number of theories to this. First, pain in the flank may not necessarily be caused by the calyceal diverticuli stone, and relief of pain may be related to improvements in musculoskeletal back pain. Another theory is that the fragmented stones maybe less symptomatic than the actual stones.

Ureteroscopy

Outcomes from ureteroscopy have been equivocal with stone-free rates of 19% to 58% and symptom-free rates of 38% to 68%.^{46,47} There are a number of technical challenges associated with ureteroscopy for the treatment of diverticular stones. An infundulotomy will often need to be performed. This has the dual purpose of allowing access to the stone and also to externalize the calyceal diverticulum into the pyelocalyceal cavities.⁴⁸ Lower pole diverticuli are difficult to treat, as there are limits to the deflection of the flexible ureteroscopes. The complications associated with retrograde management of diverticula include bleeding, cautery-induced tissue injury, ureteral perforation, and infection.

PCNL

PCNL is the favored treatment option for calyceal diverticular calculi. Stone-free rates are in the range of 70% to 100% and recurrence rates of 0% to 30%.^{40,49,50} Apart from rendering the diverticuli stone-free, PCNL allows for the fulguration/ablation of the diverticuli and either an infundibuloplasty or the ablation of the infundibulum.⁴⁸

Percutaneous access can be achieved directly into the diverticulum or indirectly via a neighboring calyx following the wall of the diverticulum that is perforated or the diverticulum is accessed via a retrograde fashion.⁵¹ The direct approach is usually favored, as it provides better stone-free rates⁵² and as such the indirect approach is usually reserved for small diverticuli or upper pole diverticuli. In situations in which the infundibulum is stenotic, a variation of the direct access involves the creation of a neoinfundibulotomy. In this instance, the diverticuli is accessed and the access needle is further advanced into the main collecting system. Both the access tract and a neoinfundibulum are dilated. The stone is then cleared and a nephrostomy tube is advanced beyond the neoinfundibulum into the renal pelvis and kept in place for a week to allow for epithelialization of the neoinfundibulum.⁵³

PCNL can be challenging, as the diverticuli are usually small and the infundibulum can be difficult to locate if there is a plan to do an infundibulotomy. Percutaneous access to anterior diverticuli can also predispose to increased bleeding from the longer distance that the tract has to traverse through renal parenchyma.

Laparoscopy

There have been a few case series of laparoscopic extraction of diverticular stones. Most of these studies have small numbers. Miller and colleagues,⁵⁴ in a study of 5 patients, managed to achieve 100% stone clearance and fulguration of the diverticular cavity and infundibulum. This technique has more relevance for calyceal stones with thin overlying parenchyma. Laparoscopy, however, is far more morbid than the other options and should be reserved only for anterior calyceal stones with thin overlying parenchyma.

In conclusion, for stones smaller than 1 cm with a short and wide infundibulum in patients who would prefer the least-invasive means of stone clearance, ESWL would be a treatment option. Ureteroscopy would be an alternative to ESWL in these same circumstances and would likely achieve a higher stone clearance rate in the appropriately selected patient. For larger stones or stones with narrow infundibuli, PCNL would give

the best stone clearance rates with the additional ability to fulgurate and ablate the diverticular cavity. Laparoscopy should be reserved for larger stones in anterior calyces with thin overlying parenchyma and in which laparoscopic experience is available.

TRANSPLANT KIDNEYS

The incidence of calculi in transplant kidneys ranges from 0.4% to 1%.^{55,56} These calculi can occur de novo or could have been present in the preoperative donor kidney. There are a number of factors that may predispose the donated kidney to stone formation. Patients with chronic kidney disease often have secondary or tertiary hyperparathyroidism. This predisposes the patient to have hypercalcemia and consequent hypercalciuria. Nonabsorbable sutures can also act as a potential nidus for stone formation if mistakenly used during the transplantation. Additionally, the immunocompromised state of the patient may predispose to recurrent UTI and subsequent infection of stones.⁵⁷

The most common stone type is calcium oxalate. Cyclosporine A used as an immunosuppressant can predispose toward hyperuricosuria. The urate in urine can act as nidus for calcium oxalate stone formation. Uric acid stones are relatively uncommon probably owing to the concentrated alkali production often seen in transplant kidneys.⁵⁵

The transplant kidney is in essence a solitary kidney and it is paramount that calculi be aggressively managed in these patients to prevent obstruction and its sequelae. These patients are especially susceptible to the loss of the renal unit, as they are more prone to infections.⁵⁸

Calculi in transplant kidneys often present late. The transplant kidney is not innervated, so pain is not a typical symptom of obstruction, although the patient may complain of vague discomfort around the graft site from the stretching of the pseudocapsule during hydronephrosis. Presentations may include fever without localizing signs, hematuria, decreased urine output, and rising serum creatinine levels.⁵⁷ It is important to have a high index of suspicion in such instances.

Imaging can also be difficult. Because of its pelvic location, KUB x-rays may not be able to visualize the stone because of the overlap with the pelvic bones. Ultrasounds of the graft may not yield good images because of the possibility of overlapping gas shadows.⁵⁶ CT scans are the most useful imaging modality to determine the presence of calculi.

Observation

Observation of renal calculi in transplant kidneys should be reserved only in a select group of

patients. Klingler and colleagues⁵⁹ successfully observed patients with nonobstructing stones smaller than 4 mm. As the kidney is denervated, pain is often not an early sign of obstruction. These patients will have to be followed closely with serum creatinine levels. The role of serial imaging is not well defined in this population but ultrasound imaging may offer the best compromise, as there is no risk of ionizing radiation and new dilatation of the renal pelvis would be a definitive sign of obstruction. The threshold for intervention in this group should be very low.

ESWL

The transplant kidney, owing to its location, offers unique challenges to ESWL as a treatment modality. The graft kidney overlies the pelvic bones and the treatment will have to be performed in the prone position. Unlike the horseshoe kidney, the graft kidney usually lies anterior to bowel, although there may be instances in which there may be interposed bowel. This would limit the efficacy of the shockwaves and possibly lead to trauma to the overlying bowel. Challacombe and colleagues,⁵⁵ in a small series, treated 13 patients with ESWL; 8 required adjuvant treatments, such as stents and percutaneous nephrostomy tubes or repeat shockwaves, to achieve stone free status. Klinger and colleagues⁵⁹ in a separate study treated 7 patients successfully with ESWL, although 3 required percutaneous nephrostomy tubes. Both studies indicate that ESWL can be efficacious for stones smaller than 1.5 to 2.0 cm. The threshold to the use of stents and nephrostomy tubes should be low, as steinstrasse would be a serious complication in the solitary transplant kidney.

Ureteroscopy

Anatomy of the transplant kidney plays an important part in the success of ureteroscopy for stones in transplant kidneys. First, localizing and access of the transplant ureteric orifice can be a challenge. This may be found in the dome or anterior surface of the bladder. The orifice and ureter may be tortuous, especially if the transplant ureter is long and redundant. Special catheters like the cobra (Fig. 7) and kumpe catheter (Fig. 8) may be required to gain access to the renal pelvis. A curved tip hydrophilic wire with good torque control can greatly help with access to the system. Newer flexible ureteroscopes with good secondary deflection will help especially with access to the lower pole calyces. Del Pizzo and colleagues⁵⁷ successfully treated 6 of 7 patients and more recently, Basiri and colleagues⁶⁰ reported a 67% success rate.



Fig. 7. A 6F cobra catheter.

Hyams and colleagues⁶¹ also described a nondilating antegrade approach to the ureteroscopic management of the transplant lithiasis. Briefly, percutaneous access was obtained before ureteroscopy. A wire was then passed down the nephrostomy tube and passed down into the bladder with the aid of an angiographic catheter. A safety wire was then placed with the aid of a coaxial catheter and the nephroscope could then be advanced into the collecting system antegradely via one of the wires. An access sheath was used based on the surgeon's discretion.

PCNL

The approach to PCNL is similar to a pelvic kidney but in a more anterior location.⁶² The patient is placed supine and access is best achieved with an ultrasound-guided or CT-guided puncture, as there is risk of overlying bowel.^{58,63} Another important aspect to PCNL of a transplant kidney is the tough fibrous capsule that forms around transplant kidneys. Coaxial metal dilators may be more efficacious at breaching this tough fibrous capsule.^{63,64} For transplant ureteral stones, these can be quite often treated without requiring tract dilation in an antegrade manner with a flexible ureteroscope.⁶¹



Fig. 8. A 5F kumpe catheter.

The kidney is fixed in its capsule and excessive torque could lead to massive hemorrhage. Flexible nephroscopes and ureteroscopes along with baskets should be used liberally to clear the stones.⁵⁵ Riffaoglu and colleagues⁶⁵ reported on 15 anterior PCNL cases performed for transplant kidneys. They achieved 100% success rates with the liberal use of flexible scopes and baskets.

Potential complications include bleeding, urosepsis (as the patients are immunocompromised), and delayed wound healing (secondary to concomitant steroid therapy), which can lead to prolonged urine leaks.

In summary, conservative management of stones in the kidney should be taken with caution. This should be reserved for stones smaller than 4 mm, and close follow-up is required; there should be a low index of suspicion for intervention. ESWL or ureteroscopy is possible as a first-line treatment for stones smaller than 1.5 cm in diameter. There should be a low threshold to stenting, as steinstrasse could have catastrophic consequences for these patients. PCNL should be considered in stones larger than 1.5 to 2.0 cm.

CROSS-FUSED RENAL ECTOPIA

The incidence of ectopic kidney is 1:2000. There are 6 different kinds of ectopia, most (90%) being fused, with the orthotopic kidney cephalad (**Fig. 9**). There is usually some degree of malrotation that places the parenchyma posterior and the pelvis anterior, not unlike a horseshoe kidney. This can lead to hydronephrosis purely from malrotation; however, other causes can be associated with UPJ obstruction or vesicoureteric reflux.

Owing to the variety of ectopias, most of the literature is based on case reports and an emphasis is made on the individualization of treatment based on anatomy. A CT scan is an important prerequisite, as it helps delineate rotation and other aberrant anatomy and is thus the most appropriate imaging modality for treatment. For example, in a patient with an anterior pelvis, distension of the pelvis may bring it up to the anterior abdominal wall, allowing an anterior supine PCNL with the aid of fluoroscopy. To achieve a successful and safe access, the C arm would have to be placed in full lateral so that the distance

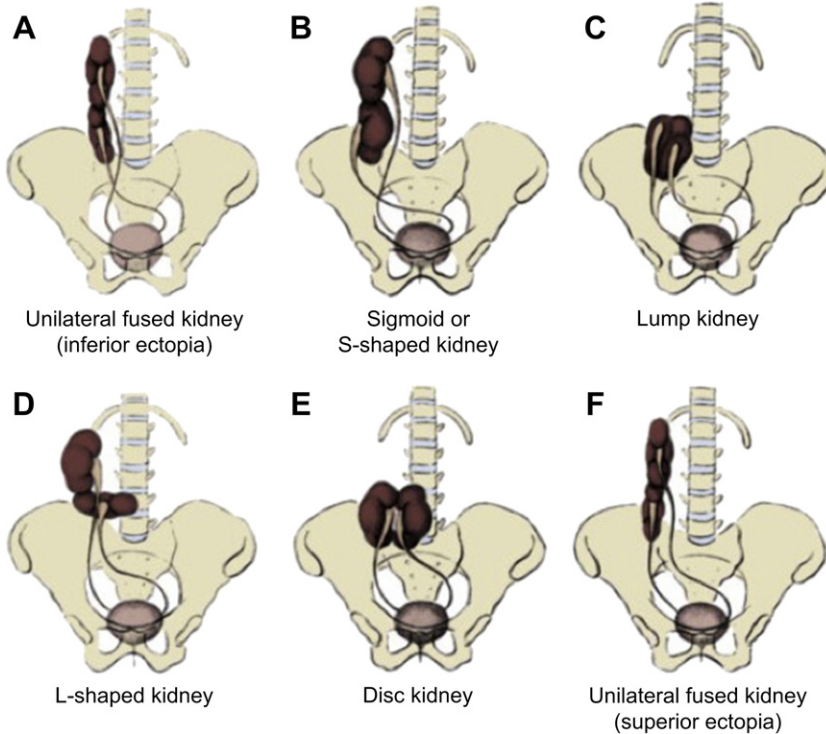


Fig. 9. Cross-fused ectopia. (A) Unilateral fused kidney (inferior ectopia). (B) Sigmoid or S-shaped kidney. (C) Lump kidney. (D) L-shaped kidney. (E) Disc kidney. (F) Unilateral fused kidney (Superior Ectopia). (Reprinted from Shapiro E, Bauer SB, Chow JS. *Anomalies of the Upper Urinary Tract*. In: Wein AJ, Kavoussi LR, Novick AC, et al, editors. *Campbell-Walsh Urology*. 10th Edition. Elsevier; 2012. Figure 117-13A-F; with permission.)

between the dilated pelvis and the anterior abdominal wall can be appreciated to avoid bowel injury.

Other approaches have involved laparoscopy, ureteroscopy, and ESWL. Tokgoz and colleagues⁶⁶ reported on 2 patients with L-shaped kidneys treated with ESWL. They achieved success in 1 patient with a renal pelvis stone after 3 ESWL sessions. The other patient failed treatment and required ureteroscopy.

Laparoscopy has also been attempted. Modi and colleagues⁶⁷ performed a transperitoneal laparoscopic pyeloplasty and pyelolithotomy on a pediatric patient with stone-free status up to the 6-month follow-up.

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

ADPKD is one of the most common inheritable diseases affecting 1:500 to 1:1000 live births.⁶⁸ It is a proliferation of tubular epithelial cells leading to blockage of the tubules and subsequent cyst formation. There are 2 variants: the polycystin-1 (PKD-1) mutation is associated with onset of cysts at an earlier age and end-stage renal failure by the fifth or sixth decade of life.

Nephrolithiasis in ADPKD is 5 to 10 times more common than in the general population.⁶⁹ There are both anatomic and metabolic reasons for this. The polycystic kidney often has urinary stasis and poor outflow by virtue of enlarging cysts that obstruct flow of urine out of the collecting system.⁷⁰ Metabolically, the urine in patients with ADPKD tends to be of low pH, citrate, and magnesium.⁷¹ This predisposes the patient to urolithiasis. Most stones in ADPKD are uric acid stones 55% to 71%,⁷² followed by calcium oxalate.

CT imaging is important in deciding what is the most appropriate modality of treatment. Open surgery used to be the standard of care,⁷⁰ but minimally invasive procedures have started to show their efficacy in small case series. There was fear that minimally invasive procedures would have increased risk of hemorrhagic cysts, loss of nephrons from shockwave, and poor stone clearance. This has not been borne out in the small case series published to date.

ESWL

Earlier experience on kidneys with cysts by Deliveliotis and colleagues⁷³ in a series of 15 patients treated with ESWL achieved an overall stone free rate of 60%. In the subgroup with polycystic kidneys, the success was 25.0% and rose to 83.3% in the subgroup with solitary cysts. This

discrepancy points to the issues of attenuation of shockwaves as they travel through the cystic medium. Also, cysts may obstruct the pelvicalyceal outflow making stone passage more difficult. Delakas and colleagues,⁷⁴ on the other hand, achieved stone-free status in 85% of 13 patients with 16 treated renal units. Most stones were smaller than 2 cm and a stent was used in 57% of the patients. There was no incidence of hemorrhagic cysts. We conclude that ESWL can be an efficacious treatment modality for stones less than 2 cm and stenting may help with overcoming the likely obstruction from the aberrant anatomy.

Ureteroscopy

There are few reports on the use of ureteroscopy for ADPKD. Liu and colleagues⁷⁵ attempted flexible ureteroscopy in 13 patients. All stones were smaller than 2 cm with a mean stone size of 5.6 mm. Most of the stones were located in the renal pelvis and on average each renal unit had 3.2 stones. There was extensive use of ureteral access sheaths and post-procedural stenting. He was able to achieve stone-free rates of 84.5% and 92.3% with a second procedure. There were 3 complications: 1 low grade fever, 1 flank pain and 1 stent-associated pain.

It seems that ureteroscopy is a viable option for stone clearance when stones are less than 2 cm in diameter with low morbidity to the patient.

PCNL

There are a number of anatomic considerations if PCNL is chosen as the method of treatment for stones in ADPKD. The aberrant anatomy owing to the presence of cysts may compress and elongate the renal calyces. This may make puncture more difficult. A number of techniques can be used to overcome this difficulty. Methylene blue can be mixed with contrast material for the retrograde pyelogram. Blue dye aspirated from the puncture needle would help confirm entry into the calyceal system. Aspiration of cysts along the access tract can also be attempted to shorten the length of the tract to the stone. Alternatively, the choice of access may have to take into consideration the calyceal anatomy. It may be more efficacious to puncture into another calyx with a wider and shorter calyx and use a flexible nephroscope to clear the stone.⁷⁶

Umbreit and colleagues⁷⁷ treated 11 kidneys with the average stone size of 2.6 cm. The investigators required 2 access tracts in 5 of the kidneys and achieved an 82% stone-free rate. There were no significant complications and no blood transfusions were required. Al-Kandari and colleagues,⁷⁶

in one of the largest studies to date, performed PCNL on 20 kidneys. Six cases had access achieved by the radiologist in the earlier part of the series. The other 13 had access achieved by the urologist. There were unable to achieve access for 1 case that eventually required an open nephrolithotomy. Three cases required second look PCNL. Most stones were larger than 2 cm. They achieved an 89.4% stone-free rate. They had 3 complications, 1 fever, 1 bleeding via the nephrostomy tract that was managed conservatively, and 1 mild postoperative hematuria.

In ADPKD, stones smaller than 2 cm are best treated by ureteroscopy or ESWL. When stones are larger than 2 cm, PCNL may be a better option. The theoretical risks of hemorrhage into cysts have not been reported in recent studies.

PREGNANCY AND STONE DISEASE

Symptomatic urolithiasis occurs in approximately 1:1500 pregnancies⁷⁸ and is comparable to the incidence in women in age-matched groups.^{78,79} Most cases occur in the second or third trimester.^{78,80}

There are a number of physiologic and anatomic changes related to increased stone formation. These include dilatation of the renal collecting system and ureters owing to the effects of compression of the gravid uterus and also smooth muscle dilatory effects of progesterone on the ureter.⁸¹ Interestingly, the predominant stone type is calcium phosphate (65.6%), as opposed to age-matched women in whom calcium phosphate comprised 34.6% of the stones.⁷⁸ This may be related to gestational hypercalciuria, hyperuricemia, and an elevated urinary pH.⁷⁸

Rosenberg and colleagues,⁸² in a retrospective review of more than 219,000 pregnancies, found 195 pregnancies complicated by urolithiasis over a 20-year span. They found that nephrolithiasis during pregnancy could be associated with recurrent abortions, mild preeclampsia, caesarian deliveries, gestational diabetes mellitus, and chronic hypertension. There was also association with urinary tract infections, hydronephrosis, and hydroureter, but surprisingly no association with preterm labor or adverse perinatal complications. This is opposed to findings from most other article, which seem to indicate increased risk of preterm labor.^{80,83} Andreoiu and MacMahon⁸⁰ found that there was a 4.3% to 14.3% incidence of premature labor in pregnant patients with symptomatic nephrolithiasis depending if intervention was performed.

One of the issues of urolithiasis in pregnancy is related to the problems of diagnosis. As mentioned earlier, dilation of the ureter and renal

pelvis may be related to the physiologic changes of pregnancy and not to the presence of obstructing calculi.⁸⁰ The use of x-rays and ionizing radiation to the unborn fetus is a concern. Currently, ultrasound is the mainstay for diagnosis. Unfortunately ultrasonography is operator dependent with an accuracy to detect stones of 56.2% and rising to 71.9% when resistive indices and presence of ureteric jets (**Fig. 10**) are incorporated into the study.⁸⁰ MR urography may be useful but its major disadvantage is that the stone cannot be directly visualized and secondary signs such as a filling defect on T2-weighted imaging, transition point of hydroureteronephrosis or double-kink signs are noted. Gadolinium is not recommended to be used in pregnancy, as there is a theoretical risk of fetal loss and long-term neurotoxicity and retardation of growth. This has been seen in animal studies,⁸⁴ but in the limited literature in humans, has not been borne out at this time.^{85,86}

There has been increasing interest in the use of low-dose CT (less than 10mSV) for the detection of stones. The issue with low-dose CT is the increase in noise, although to a certain extent this can be mitigated by newer algorithms. The best study looking at stone detection between standard and low-dose CT was a cadaveric study by Jin and colleagues⁸⁷ that showed that the sensitivity for stones smaller than 2 mm was 29% versus approximately 47% to 59% sensitivity in conventional-dose CT. For stones larger than 4 mm, most studies indicate that low-dose CT (regardless of the protocols) do provide adequate sensitivities for the pickup of calculi.^{88,89} It should be noted that none of these studies was performed in pregnancy. White and colleagues⁹⁰ looked at the issue of low-dose CT in pregnancy. In a cohort of 20 patients they picked up 13 patients with stones.

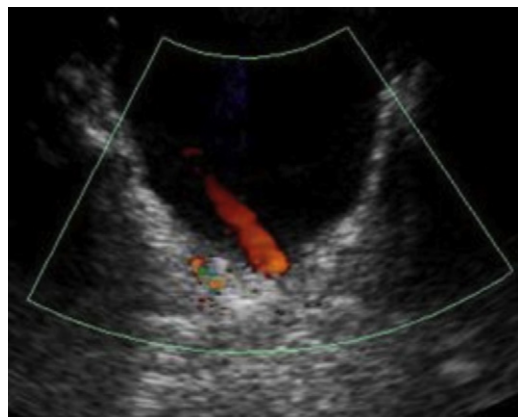


Fig. 10. Normal left ureteric jet.

Unfortunately, the sensitivity cannot be assessed, as there was no gold standard assessment of stones for obvious reasons. The American Congress of Obstetrics and Gynecology in a position paper⁹¹ states that the concern over ionizing radiation should not preclude the use of x-rays from being used if medically indicated, although nonionizing imaging modalities should be considered first. The pregnant patient should be informed of the risks and consent should be obtained before the procedure.

Conservative Management

Conservative management involves bed rest, hydration, and analgesia.⁹² Success rates range from 66.6% to 81.0%.^{78,93} Age-matched nonpregnant women on the other hand have a spontaneous passage rate of 46%.⁷⁸ Interestingly, Burgess and colleagues⁹⁴ looked at spontaneous passage rates in pregnancy and found a rate of only 48%. They defined colic as attributable to stone only if the stone was seen on imaging, observed on passage, seen during intervention, or seen in postpartum imaging. They found that up to 25% of diagnoses of renal colic did not have stones, based on their definitions. Thus, the inappropriate diagnosis of renal colic from stone could lead to the belief that stones in pregnancy have a higher spontaneous passage rate.

Percutaneous Drainage and Stenting

Ureteral stenting and percutaneous nephrostomies can be used as temporizing measures to manage symptomatic stones during pregnancy. Percutaneous nephrostomies can act as a bridge to ureteric stenting or more definitive stone management with ureteroscopy or deferring treatment until after delivery. Their advantages include effective decompression of obstruction and can be performed with local anesthesia in patients with sepsis without ureteric manipulation. Success rates are from 90% to 100%.^{95,96} Possible complications for percutaneous nephrostomies include urosepsis, hematuria, and renal hemorrhage. Also, the patient has to deal with the social consequences of having an externalized appliance. These tubes can also be dislodged and should be changed at 4-week to 6-week intervals to prevent the problem of early encrustation in pregnancy.

Ureteral stenting is another temporizing measure that can be used to relieve obstruction and symptoms of colic such that stones can then be treated after delivery. Stenting can be performed retrograde (typically with general or regional anesthesia) or antegrade, occasionally with local anesthesia. Positioning can be checked with ultrasonography⁹⁷

or limited fluoroscopy if there are difficulties with insertion. The main disadvantages of stenting include irritative stent symptoms, injury to the ureters during stent manipulation, urinary tract infections, hematuria, and stent encrustation and blockage owing to absorptive hypercalciuria and hyperuricosuria.⁹⁸ Stents should be exchanged every 4 to 6 weeks to avoid the problem of encrustation. Recurrent stent changes stand to cause more morbidity in pregnancy; thus, it is often recommended that for early pregnancy, a nephrostomy tube might be a more appropriate approach to urinary diversion and a stent for third-trimester pregnancies.

ESWL

ESWL is contraindicated in pregnancy, as the shockwaves are transmitted through the body and the fetus with the potential for fetal death.⁹⁹ There have, however, been case reports of patients having undergone ESWL without realizing pregnancy who went on to have a normal delivery and healthy baby.¹⁰⁰

Ureteroscopy and Lithotripsy

Advances in ureteroscopes and lasers have improved the outcomes of ureteroscopic management of symptomatic stones in pregnancy. Ureteroscopic management has been shown to have a 70% to 100% efficacy of stone clearance.^{97,101–103} Complications rates are similar to that of nonpregnant patients. In a meta-analysis by Semins and colleagues,¹⁰⁴ there was an 8.6% complication rate, most being Clavien grade 1 and 2. When obstetric complications were looked at specifically, there was a 4% complication rate with no fetal loss.¹⁰⁵ A number of modifications should be made to reduce the risks to mother and child. This includes increased use of spinal anesthesia or even sedation. Avoid using ionizing radiation by using ultrasound and direct visualization and only using fluoroscopy sparingly when there are access issues.^{106,107} The use of Holmium laser for stone fragmentation is recommended, as there is little dissipation of heat beyond the ureter and depth of energy penetration is less than 0.5 mm.¹⁰¹ Sound intensities generated are also less than that from electrohydraulic probes. Electrohydraulic probes are discouraged because of high peak pressures that could potentially harm the fetus.¹⁰⁸

PCNL

There are 2 case reports of PCNL in early pregnancy, both with good outcomes.^{109,110} PCNL is not recommended, however, as it typically requires

prone positioning, fluoroscopy, and general anesthesia.

In summary, nephrolithiasis can be difficult to diagnose and challenging to treat in pregnant patients. Up to 25% of patients with renal colic may be misdiagnosed with nephrolithiasis. Older treatment algorithms involving stenting and percutaneous nephrostomy tubes are fraught with problems of encrustation and require frequent changes. Newer data seem to point to the safety and efficacy of ureteroscopy as a means of treatment of stones in pregnancy.

URINARY DIVERSION

Urolithiasis in urinary diversions poses a unique challenge to the urologist. There is a predisposition to stone formation in urinary diversions with an incidence of 3% to 43%.¹¹¹ Different types of diversions have different propensities toward stone formation. For example, Terai and colleagues¹¹² found that the incidence was 12.9% in patients with Indiana pouch versus 43% in patients with Koch pouch.

The risk factors can be divided into metabolic and anatomic factors. The anatomic factors include urinary stasis, obstruction from strictures, reflux of mucous, and foreign bodies that act as a nidus for stone formation. Metabolically, diversions involving ileum are associated with a hyperchloremic metabolic acidosis. Long segments of ileum also predispose to enteric hyperoxaluria. The dual problems of bacteriuria and reflux lead to urease-splitting organisms in the upper tracts and increased urinary ammonium, phosphate, and bicarbonate. Thus, the most common stone type is struvite stone; nevertheless, there are also calcium oxalate, uric acid, and calcium phosphate stones reported.¹¹²

In view of the difficult and varied anatomy, the imaging of choice is the CT scan with and without intravenous contrast with delayed images to help define collecting system anatomy. The choice of treatment is highly dependent on the location of the stone, its size, and the type of diversion that the patient has undergone.

ESWL

ESWL is probably best used for stones smaller than 2 cm or as an adjunct to other procedures.¹¹³ The success rates range from 25.0% to 81.5%. This large disparity can be explained by patient selection. Cass and colleagues¹¹⁴ attributed the low success rate to dilatation of the upper tracts and immobility of obese myelomeningocele patients. On the other extreme Deliveliotis and colleagues¹¹⁵ managed a 63.7% stone-free rate after 1 ESWL session, which rose to 81.8% after

a follow-up session. This was a small study in which most patients were fit and had a cystectomy and ileal conduit for bladder cancer. Most of the patients did not have dilatation of the collecting system and, when it was present, it was attributed to obstruction from the stones.

If ESWL is attempted, it should be noted that there is a good chance that the patients may require some other form of antegrade or retrograde procedure. El-Assmy and colleagues¹¹³ reported a success rate of 65.6% with a single ESWL treatment; 7.4% required secondary procedures for stone treatment and another 7.4% developed complications from obstruction caused by stone fragments, requiring antegrade ureteroscopy or percutaneous intervention. In the Deliveliotis and colleagues' study,¹¹⁵ 18% of the patients required a secondary procedure. This consisted of percutaneous nephrolithotomy and an open ureterolithotomy.

Ureteroscopy

There are few studies describing the use of ureteroscopy for the management of urinary diversion stones. This can be attributed to the inherent difficulties of locating the implanted ureteric orifices. This is exacerbated if the bowel segment is convoluted. Furthermore, it can be difficult to traverse the uretero-enteric anastomosis especially if a stricture is present. Care must be taken in access to the left ureter, as it is usually slung under the sigmoid colon mesentery.

Hyams and colleagues¹¹⁶ published a series of retrograde ureteroscopy for urinary diversion stones. They achieved successful access in 75% of renal units. The highest was in orthotopic neobladders (90%) and lowest in Indiana pouches (33%). The deflection capabilities of the flexible scopes can also be impaired if the reservoirs and ureters are capacious, as buckling at a proximal part of the scope can lead to a loss of deflection of the distal tip of the scope.¹¹¹

Another approach would be a dual antegrade/retrograde approach. Delvecchio and colleagues¹¹⁷ described a technique of percutaneous puncture, passage of a wire down the ureter into the diversion, which would allow antegrade access via an access sheath.

PCNL

Percutaneous access can be challenging in patients with urinary diversion. Cannulation of the ureters for retrograde contrast can be difficult. A number of techniques can be used to overcome this problem. In neobladders, the chimney can be accessed via a flexible cystoscope and indigo

carmine given intravenously to aid in localization of the ureteral orifices. In ileal conduits, a loopogram can be performed and contrast can be allowed to reflux up into the collecting system to aid with access. Alternatively, a spinal needle (typically of small bore, such as a 22-gauge needle rather than an 18-gauge needle) can be punctured directly into the renal pelvis and contrast injected in. This would then allow the actual puncture to be performed fluoroscopically. Last, access can be performed via ultrasound guidance.

Stone-free rates following the use of PCNL with or without adjunct ESWL range from 75.0% to 87.5%.^{114,118,119} In a meta-analysis, El-Nahas and Shokeir¹²⁰ found that the adjunct use of ESWL to clear remnant stone fragments improved stone-free status from 62.5% to 87.5%. Historical complication rates in these patients was up to 38%, but a recent article had lower complication rates of 8.3%.¹¹⁸ These comprised 1 urine leak and 1 case of septicemia postprocedure.

Stones in Reservoirs

The risk factors for the formation of stones in urinary reservoirs include high residual urine volumes,

bacterial colonization, and large amounts of mucous exacerbated by insufficient flushing of the reservoir and foreign body material.

The most common approach is that of a transurethral access for neobladders and for the cutaneous diversion via the cutaneous stoma or additional percutaneous tract. A problem with continent cutaneous diversions is that the act of transcutaneous access via the stoma may disrupt the continence mechanism.¹¹¹

Another approach is a percutaneous approach to the conduit or reservoir. An ultrasound-guided or CT-guided puncture is preferred in this setting, as it is important to establish that there is no intervening bowel. The puncture can then be dilated with serial dilators or balloon dilation and laparoscopic ports or an Amplatz sheath can be inserted allowing access with a standard rigid or flexible nephroscope. There have also been descriptions of use of an endocatch bag to remove stones for more efficacious stone clearance (**Fig. 11**).¹²¹ An added advantage is that crushing the stones within the bag protects the mucosa of the neobladder or conduit. **Fig. 12** gives an algorithm to the management of these pouch stones.

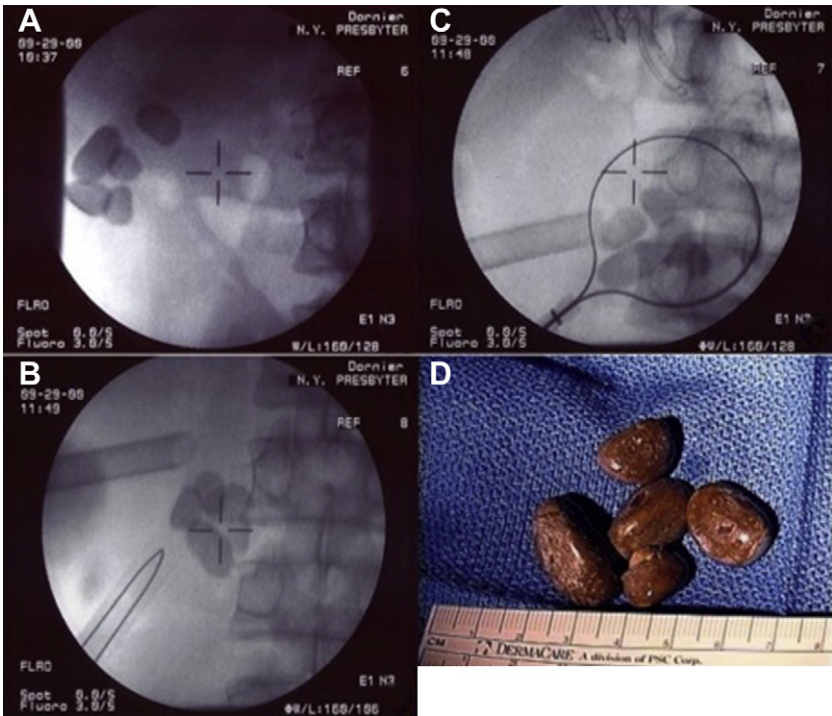


Fig. 11. (A) Stones in a continent cutaneous urinary diversion. (B) Dual access via catheterizable stoma and second percutaneous access. (C) Stones collected in entrapment bag. (D) Extracted stones.

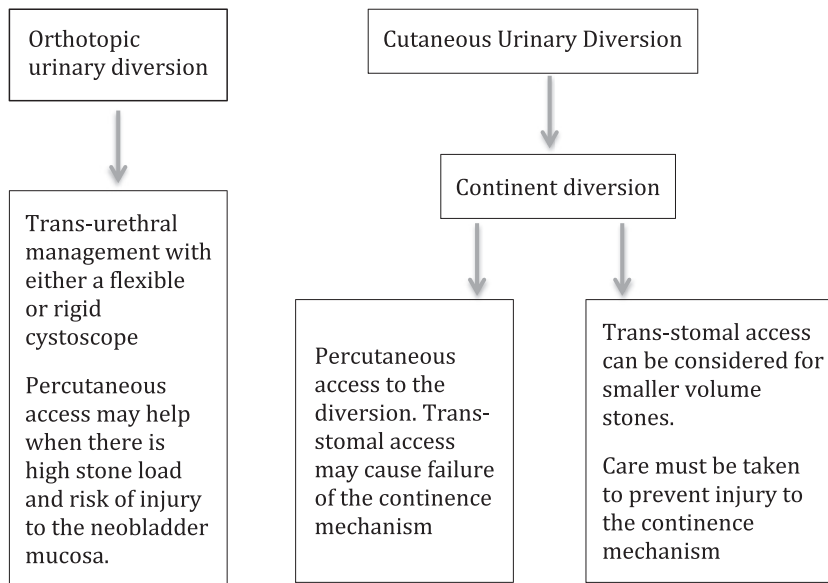


Fig. 12. Management of stones in continent urinary diversions.

SUMMARY

The management of stones in abnormal situations can be a nebulous topic; however, the principles remain the same: complete clearance of stone fragments by the least-invasive means. Treatment decisions should be individualized based on stone location, anatomic considerations, and function and location of the renal unit. Metabolic evaluation and management is especially important in this population of stone formers, as there is a high associated incidence of metabolic abnormalities.

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Advances in Percutaneous Nephrolithotomy

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KEYWORDS

- Kidney • Kidney calculi • Percutaneous nephrolithotomy • Percutaneous nephrostomy
- Post-operative imaging • Intracorporeal lithotripsy

KEY POINTS

- Percutaneous nephrolithotomy (PCNL) is increasingly applied to moderate stone burdens, particularly for stones in the lower pole calyces.
- CT can be used to obtain percutaneous access when intraoperative fluoroscopic access is considered unsafe.
- Supine PCNL is associated with reduced operative times but has not demonstrated an advantage over traditional prone PCNL.
- Liberal use of flexible nephroscopy and prone retrograde ureteroscopy can reduce the need for multiple percutaneous accesses.
- New lithotrites, including a combination ultrasonic-pneumatic device, dual ultrasonic lithotripter, and pneumatic stone breaker have the potential to enhance the efficiency of stone fragmentation and add to the armamentarium of instrumentation for PCNL.
- A trend toward the use of smaller or no nephrostomy tube post-PCNL offers the advantage of shorter hospital stay, less analgesic requirements, and reduced urine leakage without an increased risk of hemorrhage.
- New imaging modalities offer the possibility of detecting residual fragments intraoperatively and obviating secondary procedures to retrieve residual stones.

INTRODUCTION

Percutaneous nephrolithotomy (PCNL) was first described in 1976,¹ just a few years before the introduction of shockwave lithotripsy (SWL). The strong initial interest in PCNL, however, was subsequently quelled by the explosion of SWL as the first noninvasive treatment of kidney and ureteral stones. Although early on SWL was used almost indiscriminately for the management of upper tract calculi, the limitations of the technique for large and complex stones became evident over time, and PCNL became firmly established in the therapeutic armamentarium of nephrolithiasis. In recent years,

however, as the indications for ureteroscopic management of upper tract stones have expanded, ureteroscopy (URS) has, in some cases, supplanted SWL and PCNL for the treatment of some stones. Nonetheless, there have been efforts underway to reduce the morbidity and increase the efficiency and effectiveness of PCNL, making it more competitive with SWL and URS for the first-line management of upper tract stones. The contemporary advances in surgical technique, instrumentation, and perioperative care that continue to refine PCNL are reviewed here.

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INDICATIONS

One of the most important factors in selecting the optimal surgical modality for the patient with nephrolithiasis is stone size because size has been shown to strongly influence stone-free rate, need for secondary procedures, and complication rate for some treatment modalities. Historically, PCNL has been the treatment of choice for the management of large and/or complex stones. Indeed, the American Urologic Association (AUA) Guidelines for the Management of Staghorn Calculi states that “percutaneous nephrolithotomy should be the first treatment used for most patients” with stones. According to their meta-analysis of published clinical trials evaluating outcomes for surgical management of staghorn calculi, the stone-free rate for PCNL was 78% versus 71% for open surgery, 66% for combined PCNL and SWL, and 54% for SWL monotherapy. When comparing the total number of procedures required to successfully treat the stone and to manage complications, PCNL required 1.9, combination therapy 3.3, SWL 3.6, and open surgery 1.4 procedures.² Likewise, the European Association of Urology Guideline on Urolithiasis (updated Feb 2012) recommends PCNL for the treatment of all stones greater than or equal to 2 cm and lower pole stones greater than or equal to 1.5 cm.³

With improvements in the safety and efficacy of PCNL as a result of advances in instrumentation and a growing experience with the technique, some investigators have argued that the indications for PCNL should be broadened to include smaller stones throughout the kidney and specifically to those in the lower pole calyces. Deem and colleagues⁴ randomized 32 subjects with moderate sized (1–2 cm, median 1.2 cm) upper or middle calyceal or renal pelvis stones to PCNL or SWL and evaluated them at 3 months with non-enhanced CT. PCNL stone-free rate was superior to SWL (85% vs 33%, respectively) and none of the PCNL patients required a secondary procedure, whereas 77% of the SWL subjects required at least one other procedure and 17% required more than one. Quality of life, as assessed by the short form (SF)-8 quality of life survey, also favored PCNL for both mental and physical domains.

Stone location is also an important determinant of stone-free rate for some treatment modalities. Lower pole location has been shown to be associated with poor stone-free rates for SWL, likely because of limited clearance of fragments from the dependent lower pole calyces.^{5,6} On the other hand, PCNL stone-free rate is independent of stone burden.^{5–8} The Lower Pole I Study Group conducted a prospective, multicenter randomized

clinical trial (RCT) comparing SWL and PCNL for symptomatic, greater than 1.0 cm, lower pole stones and found that stone-free rates overall were threefold higher for PCNL compared with SWL (95% vs 37%, respectively, $P < .001$).⁹ When stone-free rates were stratified by stone size (less than 1 cm, 1–2 cm, and greater than 2 cm), PCNL stone-free rates were relatively uniform at 100%, 93%, and 86%, respectively, whereas SWL stone-free rates were inversely related to stone size (63%, 23% and 14%, respectively).

PCNL has increasingly been used as an alternative to URS and SWL for large, proximal ureteral stones as well. Sun and colleagues¹⁰ randomized subjects with greater than 1 cm proximal ureteral stones to PCNL or URS and found that PCNL with antegrade URS achieved a higher stone-free rate than retrograde ureterolithotripsy according to imaging obtained at discharge (95% vs 79.5%, $P = .027$) and 1 month postprocedure (100% vs 86%, $P = .026$). Several other series have corroborated these results.^{11–14}

In addition to stone size and location, other factors, including stone composition, patient factors, and renal anatomy, can influence the success of specific treatment modalities.¹⁵ SWL success is influenced by stone composition, with harder stones, such as cystine, calcium oxalate monohydrate, and brushite, being relatively shockwave-resistant; therefore, patients with these stone compositions are best treated endoscopically. Although one study suggested poorer outcomes for PCNL in subjects with increasing calcium phosphate content of their stones,¹⁶ this finding was subsequently disputed by another group¹⁷ and, in general, PCNL outcomes have not been definitively shown to be influenced by stone composition. Although predicting stone composition based on preoperative imaging has met with limited success, investigators have correlated CT attenuation coefficient (Hounsfield units [HU]) as a surrogate for stone composition with SWL success and found an inverse relationship between the two.¹⁸ Perks and colleagues,¹⁹ and others,^{20,21} have shown that harder stones, particularly those with HU greater than 900, are less likely to be successfully treated with SWL and may, therefore, be more amenable to PCNL or URS. Skin-to-stone-distance (SSD), another CT-derived parameter, has been shown to correlate with SWL success and can be used to identify patients in whom endoscopic management, PCNL or URS, is advisable.²² Perks and colleagues¹⁹ showed that an SSD greater than 9 cm is associated with diminished SWL success (79% for subjects with SSD <9 cm vs 57% for subjects with SSD >9 cm). On the other hand, PCNL is not affected by body mass index

with respect to stone-free rate, complication rate, or cost.^{23,24}

POSITIONING

PCNL has historically been performed with the patient in a prone position. Retrograde placement of a ureteral catheter before PCNL has traditionally been performed with the patient in the dorsal lithotomy position before repositioning the patient prone. The prone split-leg approach was introduced as a modification to prone positioning to increase efficiency and decrease the number of operative interventions required for patients with both upper and lower tract pathology.²⁵ This approach has become widely accepted for PCNL because it obviates patient repositioning, thereby decreasing operative time and need for operative staff for multiple patient transfers.

Another extension of the prone position is the prone-flexed position. Ray and colleagues²⁶ conducted an anatomic survey of subjects in the prone, prone-flexed (30°), and supine positions using triphasic CT. They found that the distance from the posterior iliac crest to the 12th and 11th ribs was increased by 2.9 cm and 3.0 cm, respectively ($P < .001$), with prone-flexed positioning compared with prone positioning. Consequently, in 5 of 11 subjects (45.5%) upper pole access above the 11th rib was converted to access above the 12th rib or access above the 12th rib was converted to infracostal access by using the prone-flexed position. This same group later reported on 318 subjects who underwent PCNL in the prone-flexed position and found that most (>85%) of single tract punctures of upper pole calyces could be accomplished below the 11th rib, thereby reducing morbidity.²⁷

Although prone positioning in general has proven successful, it does have notable drawbacks. Obese patients and those with cardiopulmonary comorbidities often do not tolerate being in the prone position for long periods of time. In addition, repositioning the patient from lithotomy to prone, if a split-leg table is not used, is time consuming. In an effort to overcome these drawbacks and streamline the procedure, supine PCNL was introduced.

Valdivia and colleagues²⁸ first described PCNL in the supine position in 1987 and later published a series of 557 consecutive subjects undergoing supine PCNL with favorable outcomes, including a transfusion rate of 1%, no colonic injuries, and greater than 90% of subjects describing little or no pain.²⁹ Since that time several other series of supine PCNL have been published with similar results.^{30–35}

A Cochrane-based systematic review and meta-analysis comparing supine and prone PCNL included two RCTs and two case-controlled studies that met inclusion criteria.³⁶ Operative time was shorter for supine PCNL, but complication, transfusion, and fever rates were similar for the two approaches. Only a single colonic injury was reported in the supine setting.³⁶ Another subsequent meta-analysis comparing the two approaches included the previous four studies in addition to 27 case series (8 supine and 19 prone).³⁷ This analysis also found a significant difference in operative time between the supine and prone groups (65 ± 15 minutes vs 90 ± 15 minutes, respectively, $P = .0009$) but detected no significant differences between the two groups with respect to stone-free (82% vs 82%, respectively) and transfusion rates (9% vs 4%, respectively).³⁷

Overall, the safety and efficacy of supine and prone PCNL seems to be equivalent and, at this time, there is no demonstrable advantage of one technique over the other. However, both the sample sizes and methodological quality of the studies included in the meta-analyses were limited and, therefore, a large, prospective, multicenter, RCT is needed to more reliably compare the two approaches.

In addition to the supine position, other modifications to the traditional prone position have been proposed over the years. Published series have reported on the supine oblique,³⁸ semisupine,³⁹ lateral decubitus,⁴⁰ split-leg modified lateral,⁴¹ flank,⁴² and flank prone position.⁴³ Many of these positions have demonstrated the advantage of allowing for simultaneous antegrade and retrograde access to the kidney, enabling access to stones remote from the nephrostomy tract without the need for additional percutaneous punctures.

ACCESS

The key to a successful percutaneous procedure is well-placed access into the kidney. The percutaneous puncture can be performed under fluoroscopic, ultrasound, MRI, or CT guidance, and it can be obtained from an antegrade or retrograde approach. In 2003, three-quarters of the practicing urologists in the North Central Section of the AUA who responded to a survey reported feeling comfortable performing PCNL, but only 11% of that group routinely obtained percutaneous access without the assistance of a radiologist.⁴⁴ Today, it remains true that most practicing urologists, including endourologists, in the United States do not obtain their own percutaneous renal access. Despite this, several studies have

demonstrated that access obtained by a urologist is comparable or favorable to access obtained by an interventional radiologist.

Watterson and colleagues⁴⁵ retrospectively reviewed 103 PCNL procedures at a single institution in which access was obtained by a radiologist in 54 subjects and by a urologist in 49 subjects. They found fewer complications (5 vs 15, respectively) and higher stone-free rates (86% vs 61%, respectively) in the urologist-directed access group compared with the radiologist-directed access group. Similar retrospective reviews with larger numbers of subjects have corroborated these findings.^{46,47} Tomaszewski and colleagues⁴⁸ also compared 195 subjects with urologist-directed access with 38 subjects with radiologist-directed access and found comparable complication rates between the two groups. However, the stone-free rate was higher with urologist-obtained access (99% vs 92%, respectively), and access obtained by a radiologist was considered unsuitable in 37% of subjects, necessitating access by a urologist at the time of surgery. Of note, however, access obtained by a radiologist was often done solely for the purpose of renal decompression, without the foresight or opportunity to communicate with the urologist about the suitability of the access for future surgical intervention. These data underscore the advantage of the urologist over the radiologist in obtaining appropriate access, which is that the urologist can apply his or her knowledge and expertise in renal anatomy and surgical technique to select a puncture site that minimizes the number of procedures and improves outcomes.

Intraoperative percutaneous access is most commonly performed using fluoroscopic guidance. Inherent to this modality is exposure to ionizing radiation for the surgeon, operating room staff, and patient. The dose of radiation in this setting is not inconsequential to the physicians or staff who perform these surgeries daily, or to the recurrent stone formers who often undergo repeated surgical interventions. Kumari and colleagues⁴⁹ sought to quantify the radiation exposure received by the urologist, operating room staff, and patient during PCNL using lithium fluoride thermo-luminescent dosimeter chips to monitor incident radiation exposure in 50 consecutive PCNL procedures. With a mean operating time of 75 minutes and mean fluoroscopy time of 6 minutes (1.8–12.16 minutes), the mean incident radiation exposure to the finger of the operating urologist and assisting resident were 0.28 mSv and 0.36 mSv, respectively, and to the subject was 0.56 mSv. Although the mean radiation dose at the level of the trunk of the operating urologist

was 60 μ Sv, the radiation dose to the anesthesiologist and floor nurse was minimal. Of note, the National Commission on Radiation Protection states that the maximum permissible dose equivalent for occupational exposure in 1 year for the combined whole body is 50,000 mSv. Although the average radiation exposure during PCNL described by Kumari and others⁴⁹ is well under the permissible yearly amount, it is important to keep in mind that radiation dose can vary greatly depending on complexity and length of procedure and can accumulate quickly, particularly for those urologists and/or staff largely dedicated to endourology and for those patients afflicted with chronic stone-forming conditions.

An alternative to fluoroscopy is ultrasound-guided percutaneous access. The advantages of ultrasound-guidance include lack of ionizing radiation to the patient and physician, the ability to identify nearby organs such as bowel, spleen or liver, widespread availability, and low cost. However, ultrasound-guidance is quite operator dependent and has limited ability to delineate fine detail of renal anatomy, particularly in obese patients or those with nondilated collecting systems.⁵⁰ Despite these limitations, ultrasound-guided percutaneous puncture of the collecting system is ideal for pregnant^{51–53} and pediatric patients and for those in whom retrograde placement of a ureteral catheter is difficult or impossible (eg, those with urinary diversions or renal transplants^{54,55}).

Several groups of investigators have examined the safety and efficacy of ultrasound-guided percutaneous renal access, all of which concluded that ultrasound-guided access has satisfactory outcomes with few complications and less radiation exposure compared with conventional fluoroscopic-guided access.^{56–59} Agarwal and colleagues⁶⁰ prospectively evaluated 224 subjects undergoing PCNL who were randomized to fluoroscopic or ultrasound-guided access. They found a shorter mean access time (1.8 minutes vs 3.2 minutes, $P < .01$) and fewer mean puncture attempts (1.5 vs 3.3, $P < .01$) to achieve access into the desired calyx in the ultrasound group compared with the fluoroscopy group. Furthermore, mean duration of radiation exposure was shorter for ultrasound compared with fluoroscopic guidance (14.4 seconds vs 28.6 seconds, respectively, $P < .01$) and all subjects in both groups were stone free at 1 month based on noncontrast CT.

MRI has recently been described as an alternative means of nonionizing radiation that can be used to guide percutaneous renal access.⁶¹ Kariniemi and colleagues⁶² prospectively evaluated eight subjects undergoing percutaneous access using an open-configuration, C-arm shaped MRI and reported

success in seven of the eight attempts, with the only failed attempt occurring in a nondilated system. The investigators noted that a significant drawback of this technique, however, is difficulty visualizing the guidewire with MRI.

For patients with unusual anatomy, such as spinal cord deformity in spina bifida or scoliosis, percutaneous access under fluoroscopic guidance can predispose to a higher likelihood of adjacent organ injury. In these instances, CT-guided percutaneous renal access obtained at a setting separate from PCNL provides an advantage over the traditional fluoroscopic approach. Matlaga and colleagues⁶³ reported that 3% of 154 percutaneous nephrolithotomies underwent CT-guided access because of spinal deformity, retrorenal colon, or transplant kidney, and subsequently underwent successful PCNL.

Because percutaneous renal access is not a skill set that is routinely included in the curriculum of urologic residency, some practitioners have favored using the more familiar retrograde approach to the kidney. Lawson and colleagues,⁶⁴ and Hunter and colleagues,⁶⁵ described directing a steerable catheter in a retrograde fashion into the desired calyx, then advancing a puncture wire out through the catheter to the skin, creating through-and-through access. Since their first reports, contemporary modifications of the technique have been described, including the use of endoscopic assistance to visually direct the puncture wire out through the targeted calyx.⁶⁶

Endoscopic assistance has also been used to facilitate antegrade access to the kidney when a percutaneous puncture cannot be successfully performed or when a wire cannot be navigated out of an obstructed calyx. The initial report in 1995 described the use of simultaneous retrograde URS and fluoroscopic percutaneous renal access.⁶⁷ Kidd and Conlin⁶⁸ reported three clinical scenarios, morbid obesity, renal ptosis, and a large staghorn calculus, in which endoscopic assistance was a valuable adjunct to traditional fluoroscopic or ultrasound-guided antegrade renal access. Other investigators have advocated for the routine use of ureteroscopic-guided percutaneous renal access because they argue that endoscopic-assisted access provides for safer, more precise placement of the working sheath, potentially translating into less bleeding, and that the use of a ureteroscopic access sheath facilitates drainage, passage of fragments, and easy access to calyces that are inaccessible via the nephroscope.⁶⁹ Although this technique adds to troubleshooting options available to assist with difficult access, routine use is arguably unnecessary, time-consuming, and cost-inefficient.

One of the advantages of PCNL in treating large or complex stones is the large caliber of the access tract, which allows for intact removal of large stones and the use of fragmentation devices that incorporate suction capability. However, morbidity of the procedure is often attributed to the large size of the nephrostomy tract (typically 30F). A review of data derived from the Clinical Research Office of the Endourology Society (CROES) global database of over 5000 PCNLs showed that the probability of bleeding was higher with larger caliber working sheaths (odds ratio 1.42, $P = .0001$).⁷⁰ In an effort to decrease the morbidity of PCNL, there has been interest in reducing the size of the working sheath and/or the size of the nephrostomy tube.

The technique of using a small caliber working sheath, known as the mini-perc, was originally an extension of a pediatric technique that used an 11-15 F peel-away vascular access sheath.⁷¹ Jackman and colleagues⁷² later substituted a 13 F ureteral access sheath for the flimsy vascular access sheath because of it offered superior stability. The technique involves conventional percutaneous access to the collecting system using an 18-gauge needle. After passage of two guide wires down the ureter, a 13 F sheath is passed directly over the working wire, without the need for sequential dilation. In a small series of nine mini-percs on stones with an average cross-sectional area of 1.5 cm², Jackman and colleagues⁷² reported stone-free rates comparable to standard PCNL with no transfusions and modest pain medication requirements.

Three prospective trials compared the safety and efficacy of mini-perc with standard PCNL. Knoll and colleagues⁷³ randomized 50 subjects with solitary lower pole or renal pelvic calculi to mini-perc (25 subjects, 18 F outer sheath) or standard PCNL (24 subjects, 26 F outer sheath). Of note, mean stone size in the standard group was slightly larger than in the mini-perc group (22 mm vs 18 mm) and postoperative management differed between the two groups (subjects undergoing uncomplicated mini-percs were left tubeless, while all subjects undergoing standard PCNL were left with 22 F nephrostomy tubes). Operative times, stone-free rates, and complication rates were comparable between the two groups, but the mini-perc group reported slightly lower postoperative pain scores and had a significantly shorter hospital stay (3.8 vs 6.9 days) compared with the standard PCNL group. Cheng and colleagues⁷⁴ performed an RCT that compared 72 subjects undergoing mini-perc using a 16 F sheath with 115 subjects undergoing standard PCNL using a 24 F sheath. Although mini-perc was associated with a lower

transfusion rate ($P < 0.05$), the procedure was significantly longer than standard PCNL. Finally, Mishra and colleagues⁷⁵ prospectively compared mini-perc with standard PCNL in subjects with 1 to 2 cm renal stones and found longer operative times but significantly less blood loss, lower analgesic use, and reduced hospital stay for mini-perc compared with standard PCNL.

Mini-perc is the predecessor of the microperc, a technique that furthers the concept of downsizing renal access. Bader and colleagues⁷⁶ initially described using an “all-seeing needle,” which allowed visualization of the punctured calyx and stone before proceeding with dilation to 30 F for standard PCNL. The group subsequently used this needle to obtain access and perform PCNL in a single-step. After obtaining percutaneous access with the 16-gauge all-seeing needle under optical guidance, the inner bevel of the needle is removed, leaving the 4.85 F outer sheath in place. A three-way connector is attached to the proximal end of the sheath to allow for irrigation and passage of a 200 μ m laser fiber and a micro-optic (**Fig. 1**).⁷⁷ This technique may have an advantage compared with SWL for the treatment of intermediate-sized lower pole stones because it allows for direct visualization of the stone and active clearance of fragments using pressurized irrigation. Micro-perc is applicable to stones in calyceal diverticuli and in horseshoe and ectopic kidneys.⁷⁷ Further studies, ideally in a randomized, controlled setting, are needed to define the safety, efficacy, and applicability of this innovative technique.

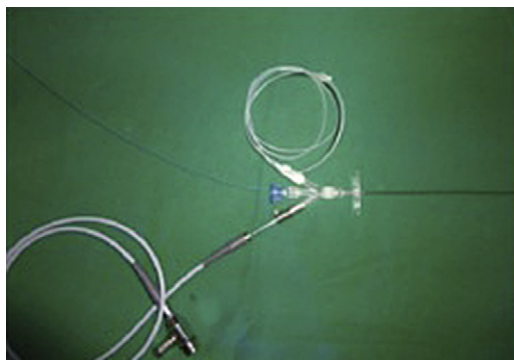


Fig. 1. Fully assembled microperc set-up, including 4.85 F needle sheath fitted with a 3-way adapter accommodating irrigation tubing above, telescope cable below, and laser fiber passing through the center of the sheath. (From Desai MR, Sharma R, Mishra S, et al. Single-step percutaneous nephrolithotomy (microperc): the initial clinical report. *J Urol* 2011;186:140–1, Fig. 2D; with permission.)

For complex stones, multiple percutaneous accesses are often needed to removal stones from disparate locations. However, the use of multiple accesses carries a higher risk of bleeding and complications, including potentially a detrimental effect on renal function, compared with single access.^{78,79} Accordingly, measures that reduce the need for multiple accesses are desirable. Wong and Leveillee⁸⁰ made liberal use of flexible nephroscopy and holmium:YAG laser lithotripsy in their series of 45 subjects with >5 cm partial or complete staghorn calculi in which a single upper percutaneous renal access was obtained. With a mean of 1.6 procedures per subject and a transfusion rate of 2.2%, they achieved a 95% stone-free rate. Other investigators have described the use of same-procedure URS to access and retrieve calyceal stones inaccessible from the percutaneous nephrostomy tract. Landman and colleagues⁸¹ reported on nine subjects with partial or complete staghorn calculi in whom a ureteral access sheath was placed before lower pole percutaneous puncture. Inaccessible stones were retrieved ureteroscopically and placed in a position where they could be removed percutaneously. They achieved a stone-free rate of 78% with an estimated blood loss of only 290 cc. Likewise, Marguet and colleagues⁸² performed initial URS and treated or displaced stones they anticipated would be remote from the planned percutaneous access tract before repositioning the subject prone and proceeding with standard PCNL using a single percutaneous access.

Finally, in another effort to reduce the number of percutaneous accesses, Miller and colleagues⁸³ described the use of a nondilated puncture to facilitate access to a stone that is remote from the nephrostomy tract for which the associated infundibulum is either not identifiable or is inaccessible. The technique involves percutaneous needle puncture directly into the stone-bearing calyx with subsequent injection of contrast-stained saline or air that can be identified endoscopically with a flexible nephroscope (**Fig. 2**). In some cases, the nephroscope can then be advanced into the stone-bearing calyx to fragment or retrieve the stone or, in some cases, the stone may be able to be irrigated out of the calyx via saline injection through the needle.

TRACT DILATION

Historically, a variety of methods have been used to dilate the nephrostomy tract, including metal telescoping Alken dilators, sequential Amplatz dilators, and balloon dilation.⁸⁴ In general, balloon dilation is thought to be quicker than fascial

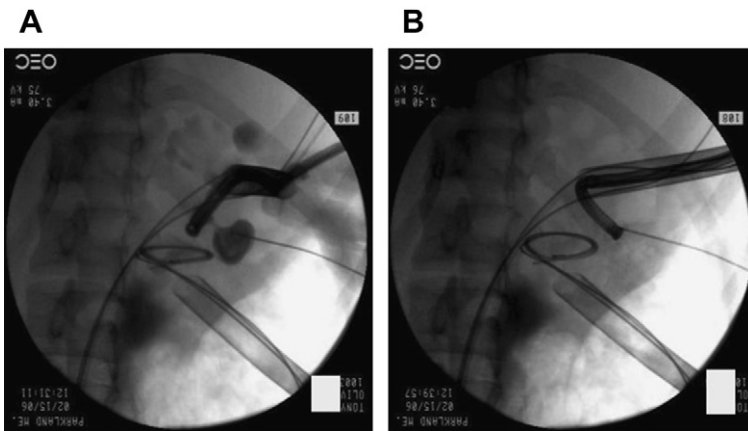


Fig. 2. Nondilated percutaneous access to facilitate identification of a stone-bearing calyx that could not be located endoscopically. (A) Percutaneous needle puncture into a stone-bearing calyx visualized fluoroscopically but not accessible with a flexible nephroscope via either of the two established nephrostomy tracts. (B) The flexible nephroscope has been advanced into the previously inaccessible calyx via an upper pole access tract after air or contrast had been injected through the needle, enabling endoscopic identification of the infundibulum.

dilation, which requires numerous passes of metal or plastic dilators. Additionally, the numerous passes that are required during dilation with sequential dilators increase the likelihood of wire dislodgement or perforation of the collecting system, which can increase the risk of hemorrhage.^{85,86} On the other hand, balloon dilation is more costly and arguably less effective in the setting of a previously operated kidney.^{87,88}

The introduction of the X-Force N30 dilating balloon (Bard Medical, Covington, GA, USA), with a burst pressure of 30 ATM (atmospheres) instead of the standard 17 ATM, offers the potential for greater efficacy in the setting of the patient undergoing reoperation. Hendlin and Monga⁸⁹ reported a 100% success rate in dilating 60 consecutive percutaneous tracts with a 30 ATM balloon compared with the historic 5% to 10% failure rate with a 17 ATM balloon.⁸⁹

Despite a general consensus in the literature regarding the superior safety and efficacy of balloon dilation over metal or plastic dilators, a recent analysis of the CROES database assessing PCNL operative times and bleeding complications in 5537 tract dilations (2277 balloon dilations and 3260 telescopic or serial dilations) demonstrated higher median operating time, bleeding, and transfusion rates in the balloon dilation group compared with the telescoping-serial dilation group.⁷⁰ Furthermore, on multivariate analysis, independent predictors of bleeding complications included sheath size, operating time, stone size, and caseload but did not include dilation method. Of note, this was not a randomized comparison, and it is possible that there are other unidentified confounding factors.

In an effort to streamline traditional two-step dilation (balloon dilation and passage of the working

sheath over the balloon), a novel device called the Pathway Balloon Expandable PCNL Sheath (Onset Medical, Irvine, CA, USA) was developed that is comprised of a polyester balloon housed in an expandable Teflon access sheath. The device allows for simultaneous tract dilation and sheath placement in one step. Pathak and Bellman⁹⁰ compared the safety and efficacy of this dilation system (Pathway Access Sheath [PAS]) to standard balloon dilation in 21 randomly assigned subjects undergoing PCNL and found a shorter insertion time with the PAS system compared with standard balloon dilation (3 minutes vs 5.7 minutes, respectively) but no significant difference in blood loss or cost. The investigators admitted that potential drawbacks to the design include a less stiff body compared with the Amplatz sheath and a slightly oblong shape, which may hinder the removal of very round stones.

LITHOTRIPSY DEVICES

Successful and efficient PCNL relies heavily on the effectiveness of the lithotripsy device. Ultrasonic lithotripsy has historically constituted the mainstay of stone fragmentation because it effectively fragments most stones and incorporates an efficient suction device for aspiration of fragments. A disadvantage of ultrasonic lithotripsy is its relative inability to effectively fragment and, therefore clear, hard stones, including those with a significant proportion of cystine, calcium oxalate monohydrate, and brushite compositions.⁹¹ Pneumatic lithotripsy is more efficient in fragmenting hard stones than ultrasonic lithotripsy, but pneumatic devices have no or limited suction capability.⁹² A dual modality device that combines both of these lithotrites, the Swiss LithoClast Ultra (Boston

Scientific Corporation, Natick, MA, USA), offers efficient stone fragmentation with concomitant suction. The device consists of a 3.3 mm diameter ultrasonic probe and hand piece as well as a 1.1 mm diameter pneumatic probe and hand piece. The hand pieces interlock, with the pneumatic probe resting within the lumen of ultrasonic probe, and the two modalities can be used together or separately. The efficacy of the Swiss LithoClast Ultra was tested in a hands-free in vitro system by Kuo and colleagues⁹³ who reported a faster mean penetration time with the combination device than either an ultrasonic or pneumatic device alone, with the pneumatic portion accounting for 79% of the total time improvement. Of note, at 100% ultrasonic power the investigators did report “occasional overheating and device malfunction.”

The CyberWand dual ultrasonic lithotripter (Gyrus ACMI, Southborough, MA, USA) is another relatively new lithotripsy device that is comprised of an ultrasonic hand piece with dual high frequency-low frequency coaxial concentric probes (2.77 mm diameter inner probe and a 3.75 mm diameter outer probe). The probes act in synergy to more efficiently comminute stones than a single probe alone while retaining suction capabilities. In a direct comparison of the CyberWand to the Swiss LithoClast Ultra in an in vitro system, the CyberWand produced significantly shorter penetration times compared with the Swiss LithoClast Ultra (4.8 vs 8.1 seconds, $P < .0001$) with no adverse events or malfunctions reported in either group.⁹⁴

In an RCT comparing the Swiss Lithoclast Ultra with a standard ultrasonic lithotripter (LUS-II, Olympus, Waltham, MA, USA) in 20 subjects undergoing PCNL, Pietrow and colleagues⁹⁵ demonstrated superiority of the Lithoclast Ultra with respect to mean time to stone clearance (21 vs 44 minutes, $P = .036$) and rate of clearance (40 mm²/min vs 17 mm²/min, $P = .028$). However, despite in vitro evidence of more efficient stone fragmentation with the CyberWand compared with the Lithoclast Ultra, a multicenter RCT of 57 subjects undergoing PCNL for greater than 2 cm renal calculi showed no advantage in the performance of the CyberWand compared with the Lithoclast Ultra with regard to time to stone clearance, stone-free rate, or complication rate.⁹⁶ The investigators did report eight device malfunctions in the CyberWand group and five in the LUS-II group that temporarily interrupted the procedures. An updated version of the CyberWand probe was released midstudy that was used for the second half of subjects in the CyberWand group. Although none of the new probes malfunctioned, subset analysis showed no improvement in stone clearance and stone-free rates with the new CyberWand.

Finally, a new device, the LMA Stone Breaker Pneumatic Lithotripter (Cook Medical, Bloomington, IN, USA) is comprised of a cordless reusable handpiece that uses CO₂ cartridges and disposable probes to generate high velocity at the probe-tip to effect stone fragmentation. Although no clinical trials have compared this device with the other available lithotrites, it is marketed for use on very hard stones.

POSTOPERATIVE DRAINAGE OPTIONS

The final surgical decision of PCNL is the need for and type of drainage tube. Historically, a large-bore catheter, such as a 24 F Councill catheter, a reentry Malecot catheter, or a nephroureteral stent, was placed at the end of the procedure and left indwelling for several days to provide drainage and tamponade the nephrostomy tract. The advantages of a large-bore catheter include reliable and efficient drainage, maintenance of the tract for a secondary percutaneous procedure, and prevention of bleeding from the tract. However, larger tubes are thought to be associated with increased patient discomfort and may in fact not limit postoperative blood loss as initially thought.

Several studies have compared the outcomes of percutaneous renal procedures using nephrostomy tubes of different sizes. Maheshwari and colleagues⁹⁷ prospectively studied 40 subjects undergoing PCNL who were left with either a 28 F nephrostomy tube or a 9 F pigtail catheter postoperatively and found a comparable incidence of hematuria in the two groups. However, the pigtail group required less analgesia and had less urinary leakage and a shorter hospital stay. Pietrow and colleagues⁹⁸ found similar results in a trial of 30 subjects randomized to postoperative drainage with either a 22 F Councill catheter or a 10 F pigtail catheter.

Wickham first described leaving no nephrostomy tube after PCNL in 1984.⁹⁹ However, the practice of omitting the nephrostomy tube fell out of favor after reported occurrences of postoperative hemorrhage.¹⁰⁰ Bellman and colleagues¹⁰¹ introduced the term “tubeless” PCNL in 1997 with their report of 50 subjects undergoing percutaneous procedures in whom the first 30 subjects were managed with an indwelling ureteral stent and 22 F nephrostomy tube that was removed 2 to 3 hours later and the last 20 subjects who were left with only an indwelling ureteral stent. These tubeless subjects were compared with a historical control group of 50 subjects drained with a standard 22 F nephrostomy tube. The tubeless group had a shorter hospital stay, lower

analgesic requirement, quicker return to normal activity, and no increased complication rate compared with the standard nephrostomy group.

The optimal choice of drainage tube after PCNL has been evaluated in randomized trials that have compared outcomes with different size or no nephrostomy tubes postprocedure. Desai and colleagues¹⁰² randomized 30 subjects to large-bore (22 F nephrostomy tube), small-bore (9 F pigtail), and no nephrostomy tube (6 F double-J stent) and found similar blood loss among the groups but the highest analgesic requirement in the large-bore group and the shortest duration of urinary leakage and shortest hospital stay in the tubeless group. Marcovich and colleagues¹⁰³ also randomized 60 subjects to 24 F reentry catheter, 8 F pigtail catheter, or double-J stent and, likewise, found no difference in blood loss or transfusion rates among the three groups. However, they discerned no advantage with regard to analgesic use or hospital stay among any the three drainage routines.

The concept of tubeless PCNL has been further tested with the introduction of the “totally tubeless” PCNL, which involves no internal or external urinary drainage tubes.^{104–106} Crook and colleagues¹⁰⁶ identified 100 PCNL procedures over a 10-year period during which the decision was made to leave no external or internal urinary drainage tube in the setting of no significant bleeding or residual stones appreciated by the surgeons. They concluded that, in the properly selected patient, a totally tubeless approach is associated with outcomes comparable to standard PCNL.

In an effort to compare the available data regarding drainage options after PCNL, several systematic reviews and meta-analyses have been performed. Zilberman and colleagues¹⁰⁷ identified 50 papers with appropriate data regarding drainage after PCNL and summarized the complications and outcomes of tubeless versus standard PCNL to create a set of recommendations regarding the indications for tubeless PCNL. They determined that major complications with tubeless PCNL were “anecdotal” and occurred in only one to two subjects per series, and they found comparable major and minor complications for tubeless and standard PCNL. However, outcomes such as cost, postoperative pain, hospital stay, and return to normal activities were all superior in the tubeless approach. The investigators concluded that nephrostomy tube placement after PCNL should be reserved for patients in whom more than two access tracts are required and/or there is significant collecting system perforation, intraoperative bleeding, likely need for second-look nephroscopy, or risk of pleural violation.

Yuan and colleagues¹⁰⁸ also performed a meta-analysis to evaluate the safety and efficacy of tubeless versus standard PCNL and identified 14 randomized, controlled trials with appropriately expressed data that were included in the analysis. Patients who underwent standard PCNL were subdivided into those managed with a small caliber nephrostomy tube (4–10 F) and those left with a large caliber tube (14–24 F). Overall, the investigators found that tubeless PCNL had the lowest analgesic requirement and shorter hospital stay compared with standard PCNL, regardless of tube size. Additionally, tubeless procedures were associated with significantly shorter operative times, reduced postoperative pain, and less urine leakage than were the small-tube group (**Fig. 3**). Although the small sample size of the small nephrostomy group may preclude meaningful comparisons, there seems to be an advantage to no nephrostomy tube compared with any size tube with regard to patient morbidity.

Finally, Wang and colleagues¹⁰⁹ also performed a meta-analysis of tubeless versus standard PCNL and identified seven randomized controlled trials from 2006 to 2010 that were included in their analysis. They found no difference in mean operative time or blood loss between the two groups but did find that tubeless PCNL was associated with lower analgesic requirements and shorter hospital stay compared with standard PCNL.

It is evident that there is an increasing trend toward performing tubeless PCNL in appropriately selected patients because of reduced patient morbidity. However, the disadvantage of losing access for second-look flexible nephroscopy in the event of residual fragments has not been fully explored. Proponents of tubeless PCNL argue



Fig. 3. Contrast-enhanced CT performed on postoperative day 1 after right tubeless PCNL demonstrates no renal hematoma or urinary extravasation. Note the nephrostomy tract and air around the right kidney.

that second-look flexible URS is as effective as second-look nephroscopy, but the likelihood that the patient actually undergoes a secondary procedure after being discharged from the hospital has not been investigated.

MANAGEMENT OF RESIDUAL FRAGMENTS

The goal of any surgical stone procedure is complete stone removal. Although the single procedure stone-free rate for PCNL is higher than for SWL or URS for comparable sized stones,^{4,9} the likelihood of residual fragments after PCNL for large renal calculi is as high as 67%, using strict CT criteria.¹¹⁰ As such, secondary percutaneous procedures to retrieve residual stones and achieve a stone-free state have been encouraged. Likewise, there has been interest in ways to enhance the identification of residual fragments at the time of initial PCNL so as to avoid the need for a secondary procedure. Portis and colleagues¹¹¹ described the use of high-resolution fluoroscopy at the time of initial PCNL to improve the likelihood of detecting and removing all fragments at the initial procedure. Among 36 subjects undergoing PCNL who were thought to be stone free, further high resolution fluoroscopy demonstrated residual fragments in 36%, resulting in an additional seven of nine subjects being rendered stone free on post-PCNL CT. However, despite these measures the stone-free rate was only 60% on postoperative CT. Portis and colleagues¹¹² further attempted to assess residual stone burden intraoperatively among 74 subjects undergoing PCNL and used their assessment of stone-free status to guide the need for nephrostomy tube placement. Based on the investigators assumption that ≤ 4 mm residual fragments can be safely left behind after PCNL, they considered their decision to place a tube correct in all cases because no subject with >4 mm residual fragments were left tubeless, and all subjects left tubeless had no or ≤ 4 mm residual fragments. However, the investigators' assumption that less than or equal to 4 mm residual fragments are harmless is subject to debate.

The natural history of fragments after PCNL largely depends on their size and location. Raman and colleagues¹¹³ retrospectively reviewed 42 subjects with residual fragments after PCNL and determined by multivariate analysis that a maximum residual stone size exceeding 2 mm and location in the renal pelvis or ureter independently predicted an adverse stone-related event at a median follow-up of 32 months. Raman and colleagues¹¹⁴ further performed a cost-effectiveness analysis and found that at their institution routine second-look nephroscopy on all patients undergoing PCNL patients

was not cost-effective and that an observational strategy for patients with less than 4 mm residual fragments was cost-effective, whereas second-look nephroscopy for patients with residual stones >4 mm in size was cost-advantageous.

POSTPROCEDURE IMAGING

Postoperative imaging after PCNL is aimed at identifying renal and extrarenal complications, such as pleural violation, colonic, splenic or hepatic injury, or urinary extravasation or hemorrhage, and at assessing stone-free status. One of the more common extrarenal complications is the occurrence of hydrothorax associated with pleural transgression during percutaneous access. Historically, many urologists have routinely obtained a chest radiograph in the postanesthesia care unit after PCNL, especially in patients who have undergone supracostal access.

Ogan and colleagues¹¹⁵ prospectively compared intraoperative chest fluoroscopy with postoperative recovery room portable chest radiography, and postoperative day 1 CT scan that included images of the lung bases in 100 subjects undergoing PCNL. They found that intraoperative chest fluoroscopy was adequate to detect clinically meaningful hydrothoraces and that it could be used to guide the need for intraoperative tube thoracostomy, thereby avoiding a delay in diagnosis and additional cost incurred with the use of routine postoperative imaging.

In an effort to reduce radiation exposure to stone patients at risk of accumulating a significant amount of radiation over their lifetimes, Bjurlin and colleagues¹¹⁶ reviewed 214 percutaneous procedures to determine whether routine postoperative chest radiography was necessary for all patients undergoing PCNL. Despite supracostal access in 21% of cases, they found an incidence of hydrothorax diagnosed by postoperative chest radiography of only 1% and both subjects were symptomatic. The investigators concluded that it is safe and cost-effective to perform selective postoperative chest radiography after PCNL, targeting those patients with supracostal access and/or those with symptomatic manifestations of potential pulmonary pathology.

Postprocedural imaging to detect residual stone burden typically includes kidney, ureter, bladder (KUB), plain nephrotomograms, CT, and/or antegrade nephrostogram. Denstedt and colleagues¹¹⁷ showed that KUB and nephrotomograms missed residual stones found at the time of second-look flexible nephroscopy in 34% and 17% of cases, respectively. On the other hand, Pearle and colleagues¹¹⁰ demonstrated that CT was 100%

sensitive and 62% specific in detecting residual stones postoperatively in a group of 31 subjects with 41 renal units evaluated prospectively with postoperative day 1 CT and flexible nephroscopy in all subjects regardless of CT findings. As such, CT constitutes the optimal post-PCNL imaging modality to detect residual fragments. Whether low-dose CT will prove to retain sufficient sensitivity to detect most residual stones remains to be seen, but it may represent a reasonable compromise that maintains high sensitivity but with reduced radiation exposure.

Cone beam CT is a novel imaging modality that uses an imaging head similar to that of a conventional C-arm but provides high-resolution axial CT-like images and may have potential future application in the setting of PCNL. Roy and colleagues¹¹⁸ described the use of this imaging modality in conjunction with PCNL to detect residual fragments intraoperatively, thereby providing the opportunity to retrieve residual stones at the time of initial PCNL and obviating the need for secondary procedures. Although the utility of this imaging modality has yet to be definitively demonstrated, it holds promise in increasing the ability to detect residual fragments intraoperatively.

SUMMARY

PCNL was developed in an effort to reduce the morbidity and mortality associated with open renal surgery but still represents the most morbid of the minimally invasive surgical modalities for stone removal. However, in recent years, efforts to reduce the morbidity and increase the effectiveness and efficiency of the procedure have brought PCNL closer to SWL and URS as the optimal first-line treatment of a variety of renal and ureteral calculi.

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The Emerging Role of Robotics and Laparoscopy in Stone Disease

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KEYWORDS

• Laparoscopy • Robot-assisted surgery • Ureterolithotomy • Pyelolithotomy • Urolithiasis • Calculi

KEY POINTS

- The prevalence of open surgical procedures has decreased dramatically with the advent of minimally invasive and endourologic procedures in the United States and world wide.
- When endourologic procedures fail, laparoscopic or robot-assisted techniques offer patients significant benefits over open surgery.
- In certain clinical circumstances such as abnormal anatomy, the need for concomitant reconstruction efforts, the unavailability of endoscopic equipment or experience, robotic or laparoscopic approaches may be considered as initial treatment options for patients.

INTRODUCTION

The surgical management for urolithiasis has undergone a dramatic clinical evolution during the past 3 decades. Advances in endoscopic equipment and procedures have relegated the practice of open stone surgery nearly to one of historical interest. The defining developments of percutaneous nephrolithotomy (PNL), ureteroscopy (URS), extracorporeal shock-wave lithotripsy (SWL), laparoscopy, and robot-assisted surgery have diminished the role of open surgery in the modern day urologist's armamentarium. The European Association of Urologists (EAU) and American Urologic Association (AUA) have released guidelines that attempt to define the roles of various surgical procedures and techniques in the spectrum of surgical stone intervention. The in-depth rationale, benefits, and morbidities associated specifically with laparoscopic and robot-assisted approaches have yet to be fully adjudicated as urologists become more facile with these procedures. The following report will discuss the historical changes from open to

minimally invasive treatment options and review the literature and indications of laparoscopic and robot-assisted approaches for the management of urolithiasis.

HISTORICAL PERSPECTIVE

Urolithiasis has plagued mankind since before recorded history; in 1901 a stone was extracted from an Egyptian mummy dating to 4800 BC.¹ During Hippocrates' era, specific surgical interventions, although crude by modern standards, were described to relieve the symptoms of stone disease.² The reports of successful stone surgery were rare in the subsequent millennia, with most procedures resulting in death and significant morbidities. In 1879, Heinke described the first pyelotomy incision with subsequent stone extraction.² During the next several decades, because of the complications associated with early attempts of nephrolithotomy, pyelolithotomy became standard therapy with the adjuvant use of blood coagulum, fibrin and fibrinogen, or cryoprecipitate to assist with the removal of calyceal stones and

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fragments.^{3,4} Smith and Boyce then described the first anastrophic nephrolithotomy for staghorn calculi in 1968, which redefined the approach to large complex kidney stones.⁵ This was predicated by the technical description by Josef Hyrtl (1882) and Max Brödel (1902) of the avascular plane of the kidney that allowed bloodless access to the renal collecting system.⁶

The recognition of ureteral calculi and their particular surgical management mirrored that of nephrolithiasis. Thomas Emmet of New York published his account in 1879 of 3 women with distally impacted ureteral stones that were treated by open ureterolithotomy, including one through a transvaginal approach.⁷ Then, in 1910, Gibson described the extraperitoneal approach to the distal ureter that remained in practice during the next century.⁷

The role of open surgical consideration has given way to a collection of techniques and technology that have minimized the subsequent mortality and morbidity for most patients requiring stone surgery. Arthur Smith labeled the new frontier of minimally invasive surgical management: endourology, or the closed controlled manipulation within the urinary tract.⁸ This shift in the treatment paradigm was established by several important developments that will only be briefly described in the context of the relevant surgical evolution. Fernström and Johansson described the first percutaneous removal of a kidney stone in 1976,⁹ which was preceded by the initial description of percutaneous nephrostomy tube placement for hydronephrosis in 1955.¹⁰ The subsequent development of an intracorporeal lithotripter in 1977¹¹ permitted PNL to become the mainstay of intervention for large renal stones. In a survey of disease codes, the annual use of PNL in the United States increased from 1.2 per 100,000 to 2.5 per 100,000 between 1988 and 2002.¹² Other surgical means of accessing the kidney and ureter for stone disease involved the development of retrograde approaches via URS.

URS was initially developed in the late 1970s to diagnosis and treat conditions of the distal ureter.¹³ The introduction of rigid, semirigid, and flexible URS has allowed the usefulness of URS to increase dramatically during the past several decades.¹⁴ This is predominantly a result of the vast technological advances made for URS stone management including miniaturization, new instruments, and lasers, in addition to the improved endoscopic skills of the urologist.

Further diminishing the role of open surgery was the development of SWL, first described by Chaussy and colleagues¹⁵ in 1980 and approved by the US Food and Drug Administration in 1984.

It has become the most commonly used therapeutic intervention for patients with upper tract stones.¹⁶ The advantages of SWL include high patient tolerance because of the infrequent need for invasive surgical procedures and minimal morbidity.

The emergence of these technologies and procedures were followed by the development of minimally invasive surgery such as laparoscopy. Clayman and colleagues¹⁷ reported the first transperitoneal laparoscopic nephrectomy in 1991, drawing attention to the capabilities of such a novel technique. Laparoscopy became an alternative to open surgery with decreased complications, less morbidity, and high stone-free rates and fostered the imagination of innovators to push the surgical envelope even further. The advanced engineering capabilities and desire to pursue remote surgery by the military gave rise to the modern day da Vinci Surgical System (Intuitive Surgical Inc, Sunnyvale, CA).¹⁸ During the past decade the US health care system has seen an explosion of robot-assisted surgical procedures. In June 2010, Jin and colleagues¹⁹ randomly surveyed 400 US hospital Web sites and found that 41% of all hospitals described robotic surgery and statements of clinical superiority were made on 86% of these Web sites. The exponential growth of robot-assisted laparoscopic techniques has provided a critical enabling technology to the surgical armamentarium, making laparoscopy possible for those not proficient in 2-dimensional spatial relationships or lacking the dexterity for precise laparoscopic maneuvers.

PATIENT CONSIDERATIONS

The prevalence of open surgical procedures has decreased significantly with the advent of minimally invasive and endourologic procedures. In the United States in 2000, only 2% of Medicare patients were treated with open surgery when they required a stone operation.²⁰ Internationally, when alternative equipment and expertise are available, open surgery is done in only 1% to 5.4% of all patients requiring stone surgery.^{20–27} Even in developing countries, the prevalence of open surgery has decreased from 26% to 3.5% of patients requiring stone surgery.^{28,29} As such, even though the prevalence of open surgery has collapsed, there remain certain clinical scenarios when it may be indicated (**Table 1**). The maturity of laparoscopic proficiency, equipment, and robotic experience has shown the ability to duplicate nearly any open surgical procedure.²⁶ The advent of robot-assisted and laparoscopic approaches, when the resources and expertise

Table 1
Clinical conditions when laparoscopic or robot-assisted surgery may be offered

Organ	Procedure	Indication
Kidney	Pyelolithotomy	Failure of endourologic management Extremely large calculi with unfavorable collecting system anatomy Need for concomitant procedure (UPJ repair)
	Nephrolithotomy	Complex staghorn calculi Unfavorable collecting system anatomy (infundibular stenosis) Ectopic or malrotated kidney making other access difficult or impossible Calyceal diverticulum with stones (particularly when located anteriorly with thin overlying parenchyma)
	Nephrectomy	Polar nephrectomy with nonfunctional portion associated with calculi Nonfunctioning renal unit with significant stone burden
Ureter	Ureterolithotomy	Large impacted stone Failure or unavailability of endourologic procedure Large stones in megaureter
Bladder	Cystolithotomy	Large stone(s) in a urinary diversion Concomitant bladder diverticulectomy with stone removal

are available, have surpassed open surgery as the preferred approach for difficult or complex cases.

Endoscopic techniques can be difficult, especially in morbidly obese individuals, when fluoroscopy may have insufficient penetration to allow adequate visualization or if the patient's weight exceeds the limits of the fluoroscopy table. If percutaneous instrumentation is not long enough to provide sufficient access to the collecting system or if the patient cannot tolerate the prone position, certain approaches to the stone cannot be safely accomplished, thereby supporting the role for laparoscopic or robot-assisted management. Also, patients with skeletal abnormalities that preclude adequate imaging or positioning are candidates for alternative options. Occasionally, patients desire a treatment that gives them the highest potential to be 100% stone free after a single procedure that URS, SWL and PNL treatments cannot guarantee. Compared with the open surgical equivalent, laparoscopic and robot-assisted laparoscopic procedures tend to require less analgesia, are associated with shorter hospital stays and less convalescence, and have improved cosmetic results.^{30–38}

APPROACHES FOR URETERAL STONES

The advent of flexible active deflection and semi-rigid ureteroscopes, digital image resolution, advances in lithotripsy devices such as the holmium:yttrium-aluminum-garnet laser, and the introduction of SWL has simplified the means and improved the outcomes for most patients requiring stone surgery while minimizing risks. The bevy of accompanying ureteroscopic

instrumentation including nitinol baskets, ureteral access sheaths, retropulsion devices, and stents have further decreased the role of open surgical approaches. Matlaga recently evaluated the contemporary practice patterns of the surgical management of urinary calculi based on surgical logs reported to the American Board of Urology (ABU) as part of certification requirements and noted that recently trained urologists tended to embrace endoscopic treatment modalities such as URS, whereas SWL was used more often by earlier trained urologists.³⁹ The combined EAU/AUA guideline recommendation on the management of ureteral calculi recognizes the value and importance of these approaches by indicating either SWL or URS as the preferred first-line intervention.⁴⁰ However, open surgery has not been completely eradicated and, by extension, laparoscopic and robotic approaches offer a preferred method of stone eradication for complex cases. The EAU/AUA panel continued to suggest that laparoscopic or open stone removal may be considered in rare cases when SWL, URS, and percutaneous antegrade URS fail or are unlikely to succeed.⁴⁰

The earliest report of laparoscopic ureterolithotomy was by Wickham in 1979 via a retroperitoneal approach.⁴¹ The role of laparoscopy was limited with only sporadic case reports until in 1992 and 1993, when technology and skills provided a foundation for broader adoption.^{42,43} The popularity also increased in developing countries where access to endourologic facilities is limited and the expense of disposable medical supplies made endourologic procedures cost prohibitive.⁴⁴

Table 2 summarizes the largest reported

Table 2
Descriptive statistics and functional results of selected laparoscopic ureterolithotomy cases (≥30 patients)

Reference No.	No. of Procedures	TP/RP	Mean Stone Size, mm	Mean Operating Room Time, min	Mean Hospital Stay, d	Stricture, %	Conversions, % ^a	Stone-Free Rate, % ^b	Urine Leak, %	Stent, %	Closure of Ureterotomy, %
45	50	TP	22.4	127.8	5.8	-	4	90	16	-	100
54	33	-	34	85	3.4	-	0	100	-	-	-
47	126	RP	13.6	88	2.8	-	2.4	97.6	2.4	100	100
55	32	RP	18.1	118	5.9	3.1	3.1	93.8	-	100	100
30	55	RP	21	108.8	3.3	5.2	18	82	Yes	64	100
56	31	RP	2.2	67	2.4	-	-	-	6.5	No	100
48	75	RP 69/TP 6	25	45	3.0	No	1.3	98.7	8	97.3	100
53	30	RP	19	121.3	-	No	3.3	96.7	3.4	3.3	100
57	50	RP	17	97	6.8	No	8	92	20	-	-
49	40	RP	22.5	92.5	6.0	-	5	100	2.5	100	100
58	74	RP 66/TP 8	18	58.7	6.4	1.4	5.4	94.6	1.4	86.5	13.5
51	101	RP 100/TP 1	16	79	3.5	4	-	92	19.8	-	-

Abbreviation: TP/RP, transperitoneal/retroperitoneal.

^a Most common cause of conversion was reported as stone migration into the kidney.

^b Stone-free rate is reported according to author's imaging test of choice at last follow-up.

laparoscopic ureterolithotomy trials in the literature. One of the few prospective randomized trials comparing laparoscopic surgery to URS or PNL for upper ureteral stones of 1 cm or larger enrolled 150 patients. The stone-free rate at discharge was highest in the laparoscopic group (88%), followed by the PNL (64%) and URS (56%) groups. Operative times were 127.8 ± 41.8 , 93.6 ± 28.9 , and 42.7 ± 2.4 minutes in the laparoscopic, PNL, and URS groups, respectively, whereas the requirement for a secondary procedure was 10%, 14%, and 22%, respectively. Two conversions to open surgery occurred in the laparoscopic group because of a dropped stone in the abdomen and an inability to localize the ureteral stone.⁴⁵ This trial shows that despite endourologic management, laparoscopic surgery may offer better single-episode stone clearance with the least need for additional procedures. Another recent prospective randomized trial supported these findings when they compared SWL, URS, and laparoscopy in 48 patients with stones greater than 1 cm (mean, 14.7 mm). They showed that laparoscopy again was associated with a higher success rate with fewer required surgical procedures than the other interventions.⁴⁶ The success rate was 35.7% for SWL, 62.5% for semirigid URS, and 93.3% for laparoscopic ureterolithotomy. One patient in the laparoscopic group required open conversion and another required a secondary PNL.⁴⁶ Although laparoscopic management may not be a first-line treatment option, it remains a valuable tool in the therapeutic algorithm.

There is debate as to the ideal approach to the ureter: retroperitoneal or transperitoneal. Qadri and associates retrospectively reported their 10-year experience with retroperitoneal laparoscopic ureterolithotomy (RLU). They had 126 patients with large or impacted ureteral stones 86 (68.25%), 28 with failed URS (22.23%), and 12 with unsuccessful SWL (9.52%). Their mean operative time was 88 minutes, and surgery was successful in 97.6% of cases with a mean hospitalization of 2.8 days and no major complications. They concluded that RLU has the ability to render a patient stone free after 1 procedure even in salvage situations.⁴⁷ Furthermore, they advocate retroperitoneoscopy to alleviate the need for bowel mobilization, retraction, the risk of inadvertent injury, and postoperative ileus. They also suggest that abdominal adhesions, shoulder pain caused by the pneumoperitoneum, and potential contamination of the abdomen with urine or blood would be avoided via the retroperitoneal approach. However, the retroperitoneum offers its own set of challenges such as the unfamiliar surgical anatomy and landmarks in the setting of

a restricted working space and the potential loss of visualization because of inadvertent peritoneotomy. Additionally, retroperitoneal access is limited by its ability to deal with upper or mid ureteral stones because exposure of the lower ureter is difficult, if not impossible.^{48,49} Transperitoneal access has been promoted to surmount these limitations and is generally more acceptable by urologists because of the familiar landmarks and a larger working space facilitating intracorporeal suturing. Bovie and colleagues⁵⁰ compared transperitoneal to retroperitoneal access for laparoscopic ureterolithotomy in 35 consecutive patients. They found that the transperitoneal approach resulted in a shorter time to access and identify the ureter (14 vs 24 minutes), ureterotomy closure (16 vs 28 minutes), and total operative time (75 vs 102 minutes). The increased retroperitoneal operative time was attributed to accidental entry into the peritoneal cavity causing a loss of pneumoretroperitoneum. There were no conversions and no transfusions required. They concluded that for surgeons learning laparoscopy, the transperitoneal approach is better, but for those with demonstrated expertise, the approach should be left to the discretion of the surgeon.

The need to close the ureter or provide drainage has not reached consensus in the literature. Gaur and colleagues⁵¹ reported that operative time for RLU was 66 minutes compared with 92 minutes if the ureterotomy was closed. They noted a prolonged postoperative urine leak in 19.8% (20/101) of patients in whom the ureter was not stented. However, of these patients, that 70% (14/20) also did not have the ureterotomy closed confounds the true impact of stenting on the risk of urine leak. They concluded that because 6 of these patients did have the ureterotomy closed, perhaps in cases of chronically inflamed, edematous, and friable ureters or after prolonged stone impaction or infection, the ureter should only be stented and left open.⁵¹ Keeley and associates described the Edinburgh experience in which 9 patients underwent a salvage transperitoneal approach for failed URS (6 patients), SWL (2 patients), or both (1 patient), 5 primarily for a large ureteral stone (mean, 27.2 mm). The average operative time was 105 minutes with a 100% success rate and no need for open conversion. Only 5 patients had their ureterotomy closed and 2 subsequently developed strictures versus none of the 9 in the unclosed ureteral group. Only 1 patient with neither a stent nor ureterotomy closure developed a urine leak requiring prolonged drainage.⁵² They surmised that as long as a drain is maintained, even in the peritoneal cavity, the ureter can be left open if a stent is also provided.

Kijvikai and Patcharatrakul⁵³ instead preferred to suture the ureter and not provide a stent in their patients and noted a 3.4% incidence of urine leak and no development of strictures. The decision on how to manage the ureter seems to be one of surgeon preference; however, it would make sense to duplicate what is done in open surgery to prevent potential complications and morbidities for patients by at least closing the ureterotomy and providing drainage to the renal unit when appropriate.

The risks associated with laparoscopic or robot-assisted ureterolithotomy deserve consideration. The most common risk is that of urine leak (0%–20%) followed by stricture formation (1.4%–5.2%).^{30,45–49,51,53–58} Ureteral strictures can develop independent of the surgical approach and may occur in up to 24% of patients after prolonged stone impaction.⁵⁹ However, several authors suggest keeping the length of the ureterotomy as short as possible to allow removal of the stone and using a cold knife instead of diathermy to create the ureterotomy.^{45,53,60} Visualization may be improved with the use of thermal energy for hemostasis at the increased risk of stricture development. Bellman and Smith also suggested that the ureterotomy be made in a longitudinal manner to prevent disruption of the ureteral blood supply.⁶¹ Visualization and vascular concerns are not the most cited reasons for open conversion; most series indicate the grounds for conversion was the inability to locate the stone or that it migrated into the kidney during the procedure. To prevent stone migration, placing some compressive device proximally on the ureter, such as a laparoscopic Babcock clamp or vessel loop, will prevent stone movement and provide an additional fixation point for the ureter during ureterotomy. The ability to locate large stones is apparent via visual cues, but for smaller impacted ureteral stones with associated inflammation or edema, this may represent a difficult aspect of the operation. It is possible to use laparoscopic ultrasonic probes to locate the stone or, alternatively, to place an open-ended ureteral catheter to the level of the stone to facilitate fluoroscopic imaging and subsequent stenting. If an open-ended catheter is placed, then a wire can be passed through the catheter with gentle manipulations to identify the corresponding section of ureteral obstruction. Gaur and colleagues⁵¹ had a large series of more than 100 patients followed for 10 years and noted the following early in their laparoscopic experience: failure to locate the ureter via RLU (>30 minutes in 30/100 cases with eventual success in 24 of these), severe retroperitoneal fibrosis making progress impossible (3/100), and one accidental ureteral

avulsion (1/100). The complications and rate of conversion decreased in time as one would expect with the maturity of the techniques and the accumulation of experience.

Any new technique or surgical procedure requires translation and adoption by the urologic community. The hurdles of this endeavor regarding how best to teach a procedure while ensuring the best possible outcomes for patients is always a challenge. The EAU has suggested that to acquire the dexterity and proficiency in laparoscopy, 50 cases are required to significantly decrease the complication rate.⁶² Fan and associates compared their first 20 RLU cases to their next 20 cases and were able to demonstrate a decrease in their operative time from 120 to 65 minutes.⁴⁹ Additionally, they had 2 cases requiring open conversion and a complication rate of 15% in their first 20 procedures compared with zero in their last 20. The arduous pursuit of obtaining the needed laparoscopic proficiency to maintain optimal patient outcomes is difficult for most surgeons. However, this is perhaps one of the clear advantages that robot-assisted laparoscopic surgery can provide. The wristed instruments and 3-dimensional vision allow greater dexterity for the surgeon in a more ergonomic situation. This can facilitate the successful transition from open to laparoscopic surgery and can flatten the learning curve.

APPROACHES FOR KIDNEY STONES

The particular techniques of laparoscopic or robot-assisted management of nephrolithiasis can be placed into one of several broad classifications of technique: pyelolithotomy, nephrolithotomy, or combined procedures (concomitant ureteropelvic junction [UPJ] repair, calyceal diverticula ablation, or partial nephrectomy). The data associated with each type of procedure will be described next.

Laparoscopic/Robot-Assisted Pyelolithotomy

Laparoscopic pyelolithotomy was introduced by Gaur and associates in 1994 with the initial description of a retroperitoneal approach in 5 patients with stones not amenable to either SWL or PNL.⁴⁴ Multiple reports since that time have documented either a retroperitoneal or transperitoneal approach with stone-free rates ranging from 71% to 100% and conversion to open surgery from zero to 27%.^{33,35} Most series tend to prefer the retroperitoneal approach because of the decreased risk of peritoneal contamination and because a posterior approach to the renal pelvis can be extended into a superior

infundibulotomy without risk or limitation of the renal vasculature. Note in most cases the renal hilar vascular anatomy overlies the anterior surface of the renal pelvis, obstructing access to the upper calyceal system. **Table 3** provides a summary of these studies. Sinha and Sharma reported their results of retroperitoneal laparoscopy for 1.6- to 2.5-cm solitary renal pelvic stones that would have been susceptible to endourologic treatment had such facilities been available. They did not close the pyelotomy in 14 of the initial patients, 2 of whom experienced a prolonged urine leak, whereas in the 6 subsequent patients, with a closed pyelotomy, no leak occurred.⁶³ Meria and colleagues⁶⁴ compared 16 patients undergoing transperitoneal laparoscopic pyelolithotomy with 16 patients undergoing PNL for renal pelvic stones greater than 2 cm. Because the stone-free rates were similar (88% vs 82%), and the laparoscopic group had longer operative times and a 12% risk of developing a urine leak, and 2 patients required open conversion, they concluded that PNL should be the primary treatment of uncomplicated large pelvic stones. However, in anomalous kidneys this may not be as clearly indicated. Tunc and colleagues⁶⁵ examined 150 patients with 57 duplicated, 45 horseshoe, 30 malrotated, 14 pelvic, and 4 crossed fused ectopic kidneys treated with SWL (Siemens Lithostar Plus; Siemens, Erlanger, Germany). The overall stone-free rate was only 68% with the corresponding kidney-specific stone-free rates of 80.7%, 66.7%, 56.7%, 57.2%, and 25%, respectively. Braz and colleagues⁶⁶ have reported an improved 81% stone-free rate for bulky stone disease at 3 months following ureteroscopic treatment, but still 62% of patients required ancillary procedures. Laparoscopic pyelotomy has been advocated because of avoidance of nephron damage and decreased risk of bleeding that may complicate PNL.⁶⁷ This may be especially important for patients who already have impaired renal function and require a procedure to give them the best chance of eradication of the stone in a single procedure. The prohibitive factor has generally been the acceptance and implementation of laparoscopic reconstructive techniques.

The limitation of the skills needed to be able to effectively suture intracorporeally with laparoscopy has always been a barrier to widespread adoption. However, robot-assisted surgery is the great equalizer providing a translation of open suturing technique to the laparoscopic environment with 3-dimensional visualization, magnification, and tremor dampening. Badani and associates published their series of 13 patients who underwent robot-assisted extended

pyelolithotomy for mostly partial and 1 complete staghorn calculi with a mean stone size of 4.2 cm in 2006.⁶⁸ All procedures were transperitoneal with no open conversions, transfusions, or urine leaks. Two of these patients required lower pole nephrotomies to render them stone free, which all patients were except for 1 who had a complete staghorn calculus. Their mean operative time was 158 minutes (range, 90–257 minutes) with a mean console time of 108 minutes (range, 60–193 minutes). The only difficulty was in extending the pyelotomy to the upper pole because of hindrance of the renal vasculature, but they thought that the wristed instrumentation gave them a distinct advantage compared with pure laparoscopic approaches.⁶⁸ In 2010, Hermal and colleagues⁶⁹ described their experience with 50 robot-assisted cases in the management of urolithiasis: 36 stone extractions with reconstructive procedures, 8 pyelolithotomies, 4 nephrectomies, and 2 nephroureterectomies. They reported complete clearance of stones in 93.1% of cases, 1 open conversion because of nonlocalization of the stone, and 1 postoperative case of prolonged hematuria resolving after selective angioembolization. Based on their extensive laparoscopic and robot-assisted surgical experience, they thought that the control, dexterity, and precision of the robot-assisted approach were superior and provided a significant advantage in reconstructive efforts.⁶⁹

One of the main concerns with robot-assisted surgery is the associated equipment, maintenance, and expense. Link and colleagues⁷⁰ developed a model of mathematical cost showing that robot-assisted pyeloplasty is 2.7 times more expensive than the laparoscopic counterpart. In contrast, an earlier report by be Gettman and colleagues⁷¹ described only a 1.7-fold increase in cost of the robotic approach and much longer operative times for the laparoscopic (235 minutes) versus the robotic (140 minutes) technique. The expense is considerable regardless whether it is 1.7- or 2.5-fold higher than laparoscopy, but it is reasonable to expect the impact of depreciation to be mitigated at high-volume robot-assisted surgery centers.

Laparoscopic/Robot-Assisted Nephrolithotomy

The feasibility of performing laparoscopic anatomic nephrolithotomy was first demonstrated by Kaouk and colleagues⁷² in 2003. In a porcine survival study, after first creating chronic radiolucent staghorn calculi (maturation for 2 weeks), the renal hilum was controlled with a laparoscopic

Table 3
Descriptive statistics and functional results of selected laparoscopic or robot-assisted nephrolithiasis cases

Reference No.	No. of Procedures	Procedure	TP/RP	Mean Stone Size, mm	Mean Operating Room Time, min	Mean Hospital Stay, d	Stricture, %	Conversions, %	Stone-Free Rate, % ^a	Urine Leak, %	Stent, %	Closure of Incision, %
⁶³	20	LAP	RP	16–25	80.2	3.6	0	20	100	10	-	30
⁶⁴	16	LAP	TP	>20	129	6.5	-	12	88	12	-	-
⁹³	56	LAP	RP	27.5	81	4.0	-	3.6	96	-	100	100
⁶⁸	13	RAP	TP	42	158	-	-	0	92.3	0	100	100
⁶⁹	8 ^b	RAP	TP	35	106	2.7	-	12.5	93.1	0	100	100
⁹⁴	5 ^c	RAP	TP	38.4	315	3.8	-	20	75	0	100	100
⁹⁵	11	LAN	TP	52	139	-	-	0	90.9	27.3	-	100 ^d
⁷⁴	5	LAN	TP	53	170	5.4	-	0	60	0	0	100
⁷⁵	15	LPS	TP	5.8	174	1.6	-	0	80	0	100	100
⁷⁶	19	LPS	TP	-	276	3.4	-	0	90	-	100	100
⁷⁸	8	RPS	TP	2–35 mm ^e	275.8	1.1	-	0	100	-	100	100
⁷⁹	13	RPS	TP	-	235.9	2.0	-	0	95.7	-	100	100
³⁶	5	LCD	RP	-	133.8	1.5	-	0	100	0	100	-
⁸⁶	3	LPN	TP	-	360	10.6	-	33	67	33	0	0
⁹¹	9	NAL	TP	29	176	3.7	-	0	100	0	100	100

Abbreviations: LAP, laparoscopic pyelolithotomy; RAP, robot-assisted pyelolithotomy; LAN, laparoscopic anastrophic nephrolithotomy; LPS, laparoscopic pyeloplasty with removal of stone; RPS, robot-assisted pyeloplasty and stone removal; LCD, laparoscopic calyceal diverticulectomy; LPN, laparoscopic partial nephrectomy for stones; NAL, nephroscopy-assisted laparoscopic pyelolithotomy; TP/RP, transperitoneal/retroperitoneal.

^a Stone-free rate is reported according to author's imaging test of choice at last follow-up.

^b One of these cases was a robotic ureterolithotomy.

^c Note all patients were adolescents with a mean age of 16.6 years, 4 with staghorn cystine stones, and 1 with concomitant UPJ repair.

^d Collecting system and renal parenchyma were closed with a single layer of 3-0 polyglactin suture.

^e No mean stone size reported, only range of stone sizes.

Satinsky clamp, allowing successful completion of the laparoscopic anatomic nephrolithotomy in all animals, closing the renorrhaphy in 2 layers.⁷² The mean operative time was 125 minutes and warm ischemia time was 30 minutes, indicating this to be a reasonable and feasible approach. This was first successfully reported in humans by Deger and colleagues⁷³ in 2004. Simforoosh and colleagues⁷⁴ reported 5 cases of transperitoneal laparoscopic anatomic nephrolithotomy, clamping only the renal artery with a laparoscopic bulldog clamp. The mean stone size was 53 mm (range, 45–65 mm), warm ischemia time was 32 minutes (range, 29–35 minutes), and operative time was 170 minutes (range, 120–225 minutes). No transfusions were needed, and the only 2 patients who were not stone free at initial procedure were stone free after subsequent treatment with SWL. Additionally, even though they closed the renal parenchyma and collecting system in 1 layer, the authors had no patient develop infundibular stenosis on subsequent radiographic evaluation.⁷⁴ The authors thought that this approach showed promise but that additional study was needed before widespread adoption.

Laparoscopic/Robot-Assisted Approaches for Urolithiasis and Concomitant Procedures

In centers of established experience in advanced reconstructive laparoscopy, the goal of stone clearance and correction of malformations in a single procedure combines surgical efficacy with minimally invasive surgery. This has most commonly been reported in situations of UPJ repair with concomitant management of renal calculi, from both a laparoscopic and a robot-assisted approach.

UPJ obstruction is an independent risk factor for the subsequent development of nephrolithiasis. Traditionally, PNL with simultaneous percutaneous endopyelotomy has been the preferred minimally invasive treatment option. However, investigators at Cleveland Clinic reviewed their series of laparoscopic pyeloplasties (117 patients) and found that 15 patients (12.8%) also underwent concomitant ipsilateral stone treatment of 1 to 21 stones per patient with a mean size of 5.8 mm.⁷⁵ They performed transperitoneal repair in 86.7% of patients and removed the stones after dismembering the UPJ and extending the pyelotomy in an average of 174 minutes. They were successful in 80% of patients with no complications or need for conversion to open surgery.⁷⁵ Confirming the excellent results, Ramakumar and colleagues⁷⁶ reported a 90% stone-free rate in 19 patients who underwent transperitoneal laparoscopic

pyelolithotomy and pyeloplasty. Srivastava and colleagues⁷⁷ treated 20 patients with laparoscopic UPJ repair and pyelolithotomy with only a 75% stone clearance rate, but after 3 patients underwent SWL and 2 underwent PNL, all were stone free at 6 months and diuretic renography was improved in 90% of patients (the other 10% had symptomatic improvement). Atug and coworkers reported the first robot-assisted experience; they performed 55 robot-assisted transperitoneal pyeloplasties in which 8 patients also had kidney stones. The number of stones ranged from 1 to more than 30 with a size of 2 to 35 mm in diameter, and they were able to achieve a 100% stone-free rate. The requirement for the management of stones at time of surgery resulted in a mean 61.7 minutes longer of operative time with no postoperative complications and a hospital stay of 1.1 days.⁷⁸ Mufarrij and colleagues⁷⁹ also retrospectively examined their series of robot-assisted pyeloplasties in 140 patients and found similar excellent stone-free and functional results. They noted that 13 required concomitant stone extraction, with 95.7% of all patients showing resolution of their obstruction and only a 7.1% major and 2.9% minor complication rate. The combined efficiency of a single procedure to clear the stone burden while correcting anatomic obstruction provides a clear indication for laparoscopic or robot-assisted techniques.

The approach to symptomatic calyceal diverticula with stones offers an additional indication for laparoscopic or robot-assisted procedures. Although the occurrences of diverticula are relatively rare, 0.2% to 0.5% of the US population, alternative management options to endourologic procedures require consideration.⁸⁰ This is especially true for anterior located diverticula when percutaneous access is difficult or impossible and previous endourologic management has failed. Gluckman and associates performed the first laparoscopic unroofing and fulguration of a calyceal diverticulum in 1993.⁸⁰ Miller and colleagues³⁶ reported their outcomes in 5 patients who underwent retroperitoneal laparoscopic management without the need for open conversion. Mean operative time was 133.8 minutes and the mean hospital stay was only 36 hours. They used various techniques of calyceal localization as none were apparent based on laparoscopic inspection of the renal surface. In 1 patient, retrograde indigo carmine was injected identifying blue discoloration resulting from the thin overlying renal parenchyma, which was unsuccessful in the subsequent patient who required intraoperative fluoroscopy to guide the nephrotomy incision. In the other cases, intraoperative laparoscopic

ultrasound was used to direct the surgeon to the appropriate site. The use of intraoperative B-mode scanning and Doppler sonography^{81,82} may be the most reproducible and reliable method of definitively identifying the avascular areas in the renal parenchyma close to the stone or dilated calices. This calyceal localization technique also allows removal of large staghorn stones by multiple small radial nephrotomies, without risking significant loss of kidney function. Most calyceal diverticula are ablated or fulgurated, but others report the use of laparoscopic figure-of-8 suture closure of the diverticulum neck,³⁶ closure with perirenal fat,⁸³ and even injection of gelatin-resorcinol-formaldehyde-glutaraldehyde glue.⁸⁴ These studies indicate the safety of laparoscopy or robotic procedures as an alternative or adjunct to endourologic procedures.

Laparoscopic nephrectomy and partial nephrectomy for stone disease are equivalent to their oncologic counterparts in terms of success and benefit to the patient. The first laparoscopic partial nephrectomy for a stone-bearing hydrocalyx (a rare situation) was reported by Winfield and colleagues⁸⁵ in 1992. They subsequently updated their experience with success in 4 of 5 similar patients.⁸⁶ Although reports in the literature about robot-assisted partial nephrectomy for stone disease are scarce, the benefits that this platform affords make it well suited for translation of laparoscopic skills to such an endeavor.

COMBINED LAPAROSCOPIC AND ENDOUROLOGIC PROCEDURES

Occasionally, rare and complex cases require more than one treatment modality to achieve the greatest level of success for the patient. Laparoscopic and robot-assisted techniques can be and are often combined with endourologic procedures for those individuals with complicated stone disease and underlying urinary abnormalities, usually for assistance in retrieving fragments.⁸⁷ Eshghi and associates reported the first use of laparoscopic guided percutaneous removal of a staghorn calculus in a pelvic kidney in 1985.⁸⁸ Such an approach allows safe retraction of overlying structures and percutaneous access in a controlled fashion under direct vision, reducing the risk of complications compared with radiographic assisted endourologic approaches. Exploitation of this technique has also been reported for patients with stones in ectopic pelvic renal units and in horseshoe kidneys with aberrant vasculature.^{32,89} In addition, laparoscopic and robot techniques facilitate antegrade stent placement while also allowing suture closure of the

nephrotomy or pyelotomy tract to prevent bleeding and urine leakage.

In most cases of endourologic assistance, nephroscopes or ureteroscopes are used to visualize different portions of the renal collecting system to allow surgeons to break up and remove stone fragments in an effort to eradicate all stones in one procedure. For example, Nadu and colleagues⁹⁰ described using a flexible nephroscope passed through a 10-mm port during laparoscopic pyeloplasty to perform laser lithotripsy and stone retrieval in 10 patients. Salvadó and colleagues⁹¹ performed cystoscopic assisted laparoscopic pyelolithotomy to remove all stone fragments in 9 patients with a mean stone size of 20 mm, mean operative time of 176 minutes, and mean hospital stay of 3.7 days. The additional irrigation posed no problems or complications for the patients. Endoscopic measures are often necessary to retrieve small fragments because fluoroscopic images through an insufflated abdomen can be challenging to interpret and identify residual fragments. The operating room constraints with laparoscopic and/or robotic equipment coupled with patient positioning and the bulk of a c-arm make the addition of fluoroscopy a challenge. The relatively small mobile endoscopy towers can be arranged to allow stone management in a complementary fashion when needed. Nadu and colleagues⁹⁰ also described a technique to help identify calyceal diverticula during laparoscopy by creating access to the renal pelvis and guiding the nephroscope into the area of infundibular stricture for obstructed hydrocalyx or the diverticula neck to guide the nephrotomy as a “cut to the light” procedure. They performed this in 2 patients and lost 2 small stones.

The fate of lost stones during laparoscopic and robot-assisted procedures deserves some consideration. During endoscopic procedures, the urinary system is a closed system, so the “wandering stone” or fragment becomes a localization issue and a minor nuisance. At open surgery, exploration and recovery of stones are easily accomplished, which generally is not the case for laparoscopy. One of the major reasons cited for the need for open conversion is to identify lost stones.⁴⁵ Although specific reports of the consequences of retained or lost stone fragments during laparoscopy or robot-assisted surgery are scarce, it is possible to draw some important lessons from the general surgery literature. In a description of lost gallstones during laparoscopic cholecystectomy, several adverse events have been reported: intraperitoneal and abdominal wall abscess formation, fistula, and prolonged fever.⁹² It should be the aim of urologic stone

procedures to maintain the principles of the open or endourologic equivalent. Lost stone fragments represent all the potential of a retained foreign object. This requires the laparoscopic or robot-assisted surgeon to take great care in ensuring all stones are removed or at least only retained in the closed urinary system if unable to treat.

SUMMARY

The surgical approach to most cases of urolithiasis is defined by endourologic techniques and technology including SWL, PNL, or URS. However, despite the numerous advantages and advances in endourology, open surgical approaches cannot be entirely replaced. Laparoscopic and robot-assisted urological surgery is increasingly replacing open surgery as a result of accumulated surgical experience. The need for open surgical management is shrinking, especially when equivalent outcomes can be achieved with minimally invasive techniques such as laparoscopy and robot-assisted surgery. The implementation and use of these approaches, when available, have further relegated the role of open surgery to that of historical interest as the benefits to patients become more apparent. Laparoscopic and robot-assisted stone surgery is not meant to compete with endourologic procedures but instead complement them and offer the patients the best possible outcomes with the lowest risks and morbidity. The skills, technology, and costs currently available limit the current adoption of these approaches, but the number of reports extolling the relative benefits is growing. The techniques will continue to have a role in the urologist's armamentarium for the modern surgical approach for urolithiasis.

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Cost-effectiveness Treatment Strategies for Stone Disease for the Practicing Urologist

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KEYWORDS

• Kidney stones • Nephrolithiasis • Cost-effectiveness

KEY POINTS

- Kidney stones have been rising in prevalence in the United States and worldwide, and represent a significant cost burden based on direct and indirect treatment costs.
- Cost-effectiveness research in this area may enable improvements in treatment efficiency that can benefit patients, providers, and the health care system.
- There has been limited research in the cost-effectiveness of surgical interventions for stone disease, despite the diverse treatment approaches that are available.
- Medical expulsive therapy has been shown to improve rates of stone passage for ureteral stones, and there is evidence that this practice should be liberalized from the standpoints of clinical and cost-effectiveness.
- Although conservative treatment following a primary stone event seems to be cost-effective, the economic impact of medical therapy for recurrent stone formers requires clarification despite its clinical efficacy.

INTRODUCTION

The prevalence of kidney stones has steadily risen in recent decades, with upward of 8% of the United States' population presently being affected.¹ The economic burden of kidney stone treatment is substantial, with annual estimates up to \$5 billion including direct and indirect costs.^{2,3} Unfortunately, despite this considerable cost burden, there has been limited investigation of the cost-effectiveness of treatment approaches to stone disease. Indeed, efforts to maximize the ratio of benefit to cost are needed to ensure that health care costs are controlled, and to enable practitioners to maintain control of their treatment options. Treatment of stone disease is a ripe area for cost-effectiveness research, given the diverse

technologies that are available, as well as variable practice patterns for both medical and surgical treatment.⁴ Impediments to cost-effectiveness research in the urological community in general, and for kidney stone treatment in particular, have included the complexity of these analyses, which require consideration of direct and indirect costs; difficulty accessing actual cost data; the need for long-term follow-up of patients susceptible to disease recurrence; institutional, regional and global variations in cost structures; and limitations of clinical research itself that does not provide clarity regarding comparative effectiveness.⁵ This article reviews existing data regarding cost and efficacy of surgical and medical interventions for stone disease to guide the individual provider in

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his or her clinical decision-making, and identifies areas in which further research is needed to clarify which strategies are cost-effective.

TREATMENT OF KIDNEY STONES

Medical Expulsive Therapy

Because most kidney stones are treated conservatively, medical expulsive therapy (MET) has been a useful tool to expedite stone passage.⁶ However, MET does incur a direct medication cost and, potentially, an "opportunity cost." If surgical treatment is delayed in a case where the stone does not pass, additional care is rendered and there is additional lost time from work. The question of cost-effectiveness of MET was explored by Bensalah and colleagues⁷ in a decision analysis. These investigators found that MET was cost-effective for distal ureteral stones even when making "worst case" assumptions of a low cost of treatment (ie, ureteroscopy), a small benefit of MET, and/or low rates of spontaneous passage. Other studies have suggested that MET may be cost-effective for mid- or proximal ureteral stones because even a small increase in the likelihood of spontaneous passage enables a cost advantage.⁸ This evidence argues for liberal use of MET; however, clinical judgment is needed to ensure that larger and more proximal stones have a lower threshold to proceed with surgical intervention. Further research is needed in the cost-effectiveness of MET versus prompt surgical treatment of stones of various sizes in different anatomic positions.

Surgical Management

Shockwave lithotripsy

Shockwave lithotripsy (SWL) has historically been the most common treatment method for small renal and ureteral stones.^{4,9} Selecting patients who are more likely to succeed with SWL may improve the clinical and cost-effectiveness of this treatment. Favorable characteristics include smaller stones, lower Hounsfield units (<1000), shorter skin-to-stone distance (<10 cm), and, in the case of lower pole stones, favorable lower pole anatomy, including infundibulopelvic angle and length.^{10,11} Also, evidence demonstrates that slowing SWL rate significantly improves treatment efficiency and reduces the cost of SWL by 50%.¹² Although extra time is required for the treatment, there is higher treatment success and less need for auxiliary treatment.

Ureteroscopy

Use of endoscopy has become more common in recently trained urologists.⁴ Although the literature comparing ureteroscopy with SWL has been

limited,⁵ studies demonstrate a clinical advantage of ureteroscopy for distal ureteral stones, with a lack of rigorous evidence to definitively compare outcomes for stones in other locations. Studies of economic outcomes of ureteroscopy versus SWL have found that, despite the heterogeneity and limited quality of the evidence, ureteroscopy may be cost-effective compared with SWL.¹³

Flexible ureteroscopy, in particular, has enabled access to all renal calyces and direct visualization and removal of stones by a retrograde approach. Options for treatment include active extraction of fragments, typically with a ureteral access sheath, or a "dusting" technique with stent placement enabling small fragments to pass spontaneously over time. There is no consensus on the optimal technique, and studies regarding the comparative effectiveness of these approaches are ongoing. Future studies of the cost-effectiveness of these approaches will need to include short-term costs (eg, operating room time, supplies) and long-term costs (eg, future stone events and/or interventions).

Although flexible ureteroscopy is effective for small-to-medium size stones, the cost of the instruments, as well as maintenance, can be substantial. Furthermore, after one repair, the risk of requiring additional maintenance increases significantly, such that it may be cost advantageous to replace a damaged scope rather than repair it repeatedly.¹⁴ There are important techniques for maximizing the longevity of flexible ureteroscopes; these are likely to benefit both the provider and health system in reducing costs and ensuring functional equipment. These include displacing lower pole stones to more accessible calyces to prevent excessive torque, ensuring that the Holmium laser fiber is not advanced through a curved scope, and taking care not to fire the laser in the channel. Also, use of nitinol devices, smaller caliber laser fibers (ie, 200 μ gm), and use of a ureteral access sheath for larger stone burdens may minimize strain on the scope.¹⁵ Careful supervision and education of trainees is needed to ensure these lessons are inculcated and the equipment is preserved. Finally, it may be that having the urology staff process and clean ureteroscopes themselves may reduce processing-related damages and save costs compared with central processing.^{14,16}

An area of investigation has been the cost-effectiveness of pretesting patients undergoing ureteroscopy. Chu and colleagues¹⁷ retrospectively studied 104 patients with upper tract (primarily ureteral) stones with a wide range of stone sizes (0.3–4 cm; median 1 cm).¹⁷ The investigators found that pretesting significantly reduced the total costs (direct and indirect) for

treatment of patients with stones greater than 1 cm, even when assuming a cost of pretesting up to 6.2 times the current cost. A limitation of this study was use of reimbursement data, instead of actual cost data. Nonetheless, there seemed to be a cost advantage for pretesting patients with larger stone burdens undergoing ureteroscopy. Additional research is needed to better delineate the cost-effectiveness of endoscopic treatments for larger stone burdens, in terms of timing of stent placement, the use of staged procedures, and comparison with alternative approaches such as percutaneous surgery.

Percutaneous nephrolithotomy

Percutaneous nephrolithotomy (PCNL) remains the standard of care for treatment of large (>2 cm) and/or complex renal calculi.^{18,19} In addition to superior stone clearance for larger burdens, there is evidence that PCNL is cost-effective for these patients.²⁰ Although PCNL does incur higher costs in the short-term based on an inpatient hospitalization and higher disposable costs, superior stone eradication leads to a long-term cost advantage.^{13,20}

Certain investigators have examined ways to further improve the cost-effectiveness of PCNL. Investigating predictors of cost of this procedure, Bagrodia and colleagues²¹ found that only stone burden independently predicted cost, and the main impact of large stone size related to the use of second-look flexible nephroscopy (SLFN). Follow-up study of the cost-effectiveness of SLFN was performed by Raman and colleagues,²² who reported that this procedure was cost advantageous for residual fragments greater than 4 mm but not for those less than or equal to 4 mm, based on future risk of stone events requiring treatment. The investigators discussed how their cost benefit analysis was dramatically influenced by assumptions regarding likelihood of stone events, the need for surgical treatment, and surgical costs.

There is also some evidence that increased surgical experience enables more efficient and effective treatment of PCNL. Hyams and colleagues²³ reported a lower rate of 30-day mortality and ICU hospitalization for high-volume providers in a Maryland state database. Also, increased surgical experience has been associated with decreased operative time, which may have cost implications.²⁴ This may also reflect the experience of the operating room staff because troubleshooting instrumentation for PCNL and overall efficiency can be improved with experienced personnel. Finally, operating and fluoroscopy time have been showed to decrease up to 60 cases within a learning curve.²⁵ These data

suggest that referral for treatment of PCNL to higher volume providers and/or institutions may be cost advantageous, though additional research in this area is needed.

The cost-effectiveness of PCNL has been compared with ureteroscopy for treatment of larger renal stones. Hyams and Shah²⁶ recently demonstrated lower cost associated with ureteroscopy for 2 to 3 cm stones versus PCNL in a retrospective analysis with medium term follow-up. Higher cost for PCNL was based primarily on a high rate of second-stage treatment with PCNL, though there was superior stone clearance in this group of patients. The investigators framed a trade-off in cost and stone-free rate, with the caveat that long-term follow-up was needed to assess the need for future interventions in patients with small residual fragments. The investigators concluded that, although PCNL was the standard of care, the cost-profile and clinical outcomes of ureteroscopy made it a reasonable option for patients with contraindications to or preference against percutaneous surgery.

In patients with bilateral large stone burdens, it is not clear whether simultaneous or staged PCNL is cost-advantageous. There has been one study in this area by Bagrodia and colleagues,²⁷ who reported that synchronous bilateral PCNL decreased cumulative operative room time, length of stay, and cost, and thus was advantageous to patients and third-party payers. The investigators noted that physician reimbursement was significantly less compared with staged procedures, providing a disincentive to perform this procedure. This is an important point because a reimbursement scheme can influence practice patterns and provide a disincentive to render care that might be a cost-effective approach overall.

Finally, tubeless PCNL has become increasingly popular to decrease the morbidity and hasten the recovery from PCNL without conceding patient safety. Literature has demonstrated improvements in hospital stay, postoperative analgesic use, and urinary leakage, as well as in operative time.^{28,29} Although tubeless procedures may be cost-effective in properly selected patients, investigation in this area is needed because these patients frequently have ureteral stents placed and may have subsequent retrograde procedures and/or SWL.

Prevention of Kidney Stones

Primary prevention

Primary prevention of stone disease has been considered in populations that may be at increased risk based on geography (ie, warmer climates),

familial or medical risk factors, genetic testing, or changes in environment (eg, military deployment).^{8,30} Lotan and Pearle³¹ investigated the cost-effectiveness of primary prevention strategies using a decision-analysis model. They found that primary prevention of stones may be cost-effective depending on assumptions of cost, risk, and efficacy. Specifically, an intervention would be cost-effective if the incidence of disease was at least 1%, cost did not exceed \$20 per person per year, and the strategy was at least 50% effective at stone prevention. Thus, these interventions may be worthwhile in certain populations, depending on risk, because there are low-cost interventions, such as education regarding water consumption, which can be considered.³¹ Indeed, Lotan and colleagues³⁰ reported a cost model in which increased water intake would theoretically be cost-effective for a national payer system for prevention of stone disease.

Secondary prevention

First-time stone formers generally are counseled on conservative treatment measures, including dietary manipulations, to decrease risk of recurrence. These inexpensive interventions include increased water intake³² and dietary changes that have been shown to modulate stone risk.^{33,34} For recurrent stone formers, conservative treatment is generally insufficient because of the high rate of recurrence.³⁵ Medical therapy is considered in these patients and has been shown to reduce risk of recurrence in certain patients.^{36,37} Importantly, however, these medications have side effects, inconvenience, and cost that can affect patient compliance.^{8,20,38} Although older studies found that screening and treating stone patients with medical therapy lowered costs,^{39,40} these studies did not necessarily account for the benefit of conservative treatment alone, the costs of metabolic evaluation, and that not all recurrent stones necessitate treatment.⁴¹ Nonetheless, more recent studies have concluded that medical treatment in known stone formers is likely to be cost-effective depending on assumptions regarding effectiveness, cost of therapy, and rate of stone recurrence.²

Lotan and colleagues³⁵ investigated the cost-effectiveness of conservative therapy versus drug treatment for first-time versus recurrent stone formers. In a decision-analysis model, they concluded that conservative treatment was cost-effective for first-time stone formers, whereas the higher cost of drug treatment strategies was justified for recurrent stone formers. Lotan and colleagues⁴¹ also performed an international comparison of cost-effectiveness of medical management strategies for recurrent stone disease.

Contrastingly, they found that dietary treatment was the most cost-effective approach because of the relatively low cost of surgery (which was required infrequently) compared with medication (which was required daily). Empiric and directed medical therapy were more effective at controlling stone disease; however, they were not cost-effective because of the low likelihood of surgical intervention and the relatively low cost of surgery. This was true except in the United Kingdom where medication costs were sufficiently low so that empiric therapy was more cost-effective than conservative therapy. Thus, improving cost-effectiveness of medical therapy requires additional research to reduce costs of medical therapy, improve compliance, identify patients who are most likely to benefit, and to improve the efficacy of medical management itself.⁸

SUMMARY

Kidney stone disease is rising in global prevalence, and the cost burden of this condition is substantial. Although cost-effectiveness considerations are typically made by policymakers, individual practitioners have become increasingly involved in these discussions so that they may affect the rising costs of care and assert control of treatment options. Although progress is being made, there are essential areas in which additional investigation is required.

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Impact of Stone Disease Chronic Kidney Disease and Quality of Life

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KEYWORDS

• Nephrolithiasis • Quality of life • Renal function • Chronic kidney disease

KEY POINTS

- Kidney stone disease can impact renal function - with the greatest risk being related to infection stones and patients with significant comorbidities including obesity, hypertension and diabetes.
- Kidney stone disease can have a significant impact on psychological distress and quality of life.
- Vigilance is warranted to permit early detection and intervention for renal insufficiency, psychological disorders, and diminished quality of life in chronic stone formers.

INTRODUCTION

Urolithiasis is a disease with rising prevalence in the United States.¹ With a growing burden, a better understanding of the disease process and methods for prevention and treatment are being widely researched. Over the years, there has been a great leap in technology for minimally invasive management of urinary stones. The era of open pyelolithotomy has passed and currently there are much less invasive treatments, such as percutaneous nephrolithotomy (PCNL), ureteroscopy (URS), and shockwave lithotripsy (SWL). Nonetheless, recurrent stone formation is still a major issue among patients with urolithiasis.² The propensity for recurrence, necessity of lifestyle change, and frequent interventions associated with urinary stone disease may significantly affect both the risk for development of chronic kidney disease (CKD) and the quality of life (QOL) of patients burdened with this disease.

Nephrolithiasis is a worldwide health problem responsible for significant economic cost to society and serious effects on QOL, affecting both men and women with a lifetime prevalence

of 13% and 7%, respectively.³ Over the past few decades, it has been shown that stone disease incidence and prevalence is steadily increasing, a trend which has been attributed to changes in diet and lifestyle. Moreover, it may be related to the increasing prevalence of obesity and diabetes mellitus, which have also been linked to kidney stone formation. Lastly, environmental changes, namely global warming, may play a role.^{4–6} In contrast, other reports suggest that the prevalence of nephrolithiasis is stable or even decreasing in the last decade in specific parts of the globe.⁷ Incidence rates peak in both male and female around the fourth decade. In terms of race and ethnicity, prevalence and incidence of nephrolithiasis seem to be highest in white individuals, followed by Hispanics, blacks, and Asian natives. However, the rates for black Americans seem to have increased specifically at older ages.⁷

The risk of recurrence after a first kidney stone episode is controversial. In the beginning of the nineteenth century, Lamson⁸ reported a wide range for nephrolithiasis recurrence rate, from 10% to 48 %. Recent uncontrolled studies show similar figures (30%–50%) within the first 5 years

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of the first stone-related event.⁹ If the follow-up period is extended to 25 years, virtually all patients are expected to have some sort of stone recurrence, corroborating the complex and heterogeneous natural history of nephrolithiasis.^{10,11} However, recent data from randomized, controlled trials suggest significantly lower rates, ranging from 2% to 5% per year. Furthermore, the risk of recurrence seems to increase with each new stone formed.¹²

Certain special patient groups may be at higher risk for impact of disease on CKD and QOL. Though the overall incidence of nephrolithiasis in renal transplant recipients is quite low (0.4%–1%), the effects can be devastating if left untreated.^{13–15} Over the past few years, interest has renewed in the impact of bariatric surgery on calcium oxalate stone disease and oxalate nephropathy. Jejunoileal bypass surgery was abandoned in the 1990s due to major complications including nephrolithiasis and renal failure in as many as 37% of patients.^{16,17} Similar concerns are arising with newer gastric bypass procedures.^{18–20} Primary hyperoxaluria often presents with symptomatic urolithiasis earlier in life when compared with the general population and have higher chances of progressing to renal failure due to their disease.^{21,22} Struvite stones, also known as triple phosphate, magnesium ammonium phosphate, or infection stones harbor a higher risk of sepsis, renal dysfunction, and death than other stone compositions.^{23,24}

Finally, cystine stones are caused by an autosomal disorder transmitted in either a recessive or a dominant manner with incomplete penetrance due to mutations that include missense, nonsense, splicing defects, frameshift, deletions, and insertions of a single amino acid residue, and large rearrangements.²⁵ Although cystinuria accounts for only 1% to 2% of all urolithiasis in adults, it is more common in children, accounting for almost 8% of renal stones in the pediatric population. Commonly, the disease manifests in the second and third decades of life and carries a higher risk of CKD.^{26,27}

Renal colic or nephrolithiasis related events account for more than 1 to 2 million emergency room visits per year, ensuing in an expensive burden to the health care system. If the number of days lost at work is considered, the scenario is even worse. Saigal and colleagues²⁸ retrospectively calculated the direct cost of stone disease based on data from a privately insured, employed population in the United States and found it to be more than 4.5 billion dollars in 1 year. After summing up conservative estimates for indirect costs, such as workdays lost due to the disease,

the amount increased to more than 5.3 billion dollars.

This article focuses on the hidden costs of nephrolithiasis: namely the impact it has on kidney function and CKD, and the QOL of patients who suffer from recurrent bouts of debilitating pain.

Nephrolithiasis and CKD

CKD is a major public health problem and affects 13% of the adult population.²⁹ CKD can be classified into five categories according to their estimated glomerular filtration rate (eGFR) (in milliliters/minute/1.73 m²) with or without renal damage for greater than or equal to 3 months. The categories, or stages, have an eGFR of (1) ≥ 90 , (2) 60–89, (3) 30–59, (4) 15–29, and (5) <15 (ml/min/1.73 m²).

With more than \$23 billion spent by Medicare in 2009 in the United States for patients on any type of renal replacement therapy or renal transplantation, significant efforts have been made to prevent and treat possible causes of CKD.^{30,31} According to the United States Renal Data System (USRDS), the prevalence of CKD has remained relatively stable over the last decade, despite the use of different formulas to calculate kidney function. In contrast, data extracted from Medicare claims for CKD demonstrate a clear increase from 3.3% in 1998 to 8.5% in 2009. Similarly, the 2005 to 2008 analysis of the National Health and Nutrition Examination Survey (NHANES) reports that the prevalence of CKD has increased to 15.1% and an incidence rate for end stage renal disease (ESRD) of 355 new cases per million population in 2009.³⁰

Although nephrolithiasis is rarely identified as a prominent risk factor for either CKD or ESRD, there are many studies that associate stone disease with varying degrees of renal insufficiency.^{32,33} The cause of renal insufficiency in patients with nephrolithiasis is multifactorial and includes renal obstruction, recurrent urinary tract infection (UTI), repeated surgical interventions, and coexisting medical disease.^{34–40} Early recognition of CKD and management of its underlying factors could help prevent several adverse effects and decrease the risk of morbidity and mortality associated with this disease, including long-term renal replacement therapy and transplantation, as well as social and psychological distress. Patients with CKD represent 0.8% to 17.5% of those presenting with urinary stone disease.^{34,35} CKD remains an uncommon event among stone formers and nephrolithiasis-related CKD accounts for only a small percentage (usually lower than

3%) of patients for whom renal replacement therapy is necessary.³⁶

It has been assumed that CKD will develop in 3 of 100,000 stone formers annually.⁴⁰ In a cohort of 171 subjects with severe idiopathic calcium stone disease, Marangella and colleagues³⁵ reported that 18% had mild renal insufficiency, with a mean GFR of 67 mL/min/1.73 m² at referral; but there was no significant decline during a mean follow-up of nearly 3.5 years. Similarly, of the 3266 subjects with nephrolithiasis reported by Worcester and colleagues,⁴¹ CKD did not develop in any of them and there was no significant decline in creatinine clearances on long-term follow-up. On the other hand, the same investigators reported that renal function decreased with age in stone formers at a higher pace than in non-stone formers.

In the general population, lower eGFR has been observed in overweight or obese patients and also in stone formers with hypertension (HTN).^{42,43} Gillen and colleagues⁴² used NHANES III of the US population to compare eGFR between the 6% who reported a history of kidney stones and the rest who did not report a history of kidney stones. Among individuals who were overweight or obese, a history of kidney stones was associated with an eGFR that was 3.4 mL/min/1.73 m² lower after multivariate adjustment. A similar association in normal-weight individuals was not evident. Vupputuri and colleagues⁴³ demonstrated that subjects who had CKD (identified by diagnostic codes) and elevated serum creatinine (SCr) levels were 1.9 times more likely to report a history of kidney stones on telephone interview when compared with matched community control subjects. Interestingly, the association was strongest in individuals without HTN and in individuals who were identified by CKD diagnostic codes for interstitial nephritis or diabetic nephropathy. Because cases were identified via hospital record review, they may have had more undiagnosed comorbidities than did control subjects. Population-based prospective cohort studies with active follow-up to determine the risk for CKD among stone formers are lacking. In a population-based historical cohort evaluation, Rule and colleagues⁴⁴ compared subjects with diagnostic codes and/or elevated SCr levels (or eGFR <60 mL/min/1.73 m²) sustained for at least 3 months with a matched control group. With a mean follow-up of 8.6 years, the risk for clinical diagnosis of CKD was 50% to 67% higher, risk for a sustained elevated SCr was 26% to 46% higher, and risk for a sustained reduced eGFR was 22% to 42% higher in the stone group. These increased risks were independent of any comorbidities associated with CKD.

Although kidney stones may be associated with future CKD, paradoxically, there is reason to believe that CKD is protective against formation of kidney stones. As GFR declines, it is followed by a fall in urine calcium excretion, an important risk factor for stone formation.⁴⁵ Indeed, evidence suggests that stone recurrence rates may be lower in stone formers with a reduced GFR.³⁵ Ironically, if kidney stones lead to CKD, the risk for stone recurrence may decrease, leading to an underrecognition of the contribution of kidney stones to the development of ESRD. It is important to distinguish stone formers in whom stones are the primary cause of ESRD from those in whom they are only a contributing risk factor. Jungers and colleagues⁴⁰ specifically investigated ESRD cases that had been attributed to kidney stones by reviewing the case histories of 1391 consecutive subjects with ESRD in France. Forty-five (3.2%) had ESRD attributed primarily or exclusively to kidney stones, with a significant proportion being attributed to struvite stones (42%). Tosetto and colleagues⁴⁶ identified a history of kidney stones in only 3.2% of 1901 subjects who had ESRD and were on hemodialysis, two-thirds of whom (2.1%) had ESRD attributed to the kidney stones. The USRDS reports kidney stones to be the primary cause of ESRD in only 0.2% (908 or 546,878) of all-incident subjects from 2004 to 2008.⁴⁷ Nevertheless, their findings took in consideration the ESRD Medical Evidence form (CMS 2728) and not a comprehensive chart review.

In a case-control study, Stankus and colleagues⁴⁸ surveyed 300 black subjects with hemodialysis for a history of kidney stones and compared findings with the 5341 black individuals who participated in NHANES III. The likelihood of self-reported past kidney stones was higher for patients with ESRD than for the population control subjects (8% vs 3%, respectively). Of the 25 subjects with ESRD and a history of kidney stones, only five had a stone episode within 5 years of starting dialysis and only two had ESRD that was primarily attributed to the stone disease. Hippisley-Cox and Coupland⁴⁹ reported an increased risk for ESRD with women (hazard ratio of 2.1), but not men, stone formers in a cohort study. In contrast, though the Olmsted County study demonstrated significant links between CKD and stone disease, there was no statistical impact on the development of ESRD or mortality.⁴⁴

STONE TREATMENT AND CKD

Gupta and colleagues³³ reported that 75.8% of subjects with urinary stone disease and CKD had undergone multiple surgical procedures for stone

treatment. These subjects also frequently had several coexisting comorbidities (diabetes, HTN, anemia and/or bleeding disorders), some of which could either lead to the development of CKD or be a manifestation of the disease. The coexistence of medical conditions associated with CKD may increase operative risk, the incidence of postoperative complications, and ultimately affect outcomes. This complex interplay between stone disease, medical comorbidities, and surgical interventions make it difficult to attribute specific risk for the development of CKD.

Jungers and colleagues⁴⁰ found that 40% of stone formers who developed ESRD had a solitary functioning kidney before developing ESRD. Although nephrolithiasis is rarely identified as a prominent risk factor for either CKD or ESRD, there are many studies that associate them with stone disease. Worcester and colleagues⁴¹ evaluated the cause of a solitary functioning kidney among 115 stone formers. The most common culprits reported were large stone burden (29%), infection (23%), and ureteral obstruction (21%). Surgical procedures were responsible for only 8% of the solitary kidneys in this group.

The evolution of minimally invasive procedures for nephrolithiasis has been scrutinized for impact on renal function. Typically an eGFR of 60 has been used as a threshold to identify iatrogenic changes in renal function after intervention.^{50,51}

SWL

SWL is widely used to treat proximal ureteral calculi less than 1 cm and renal stones less than 2 cm in diameter.^{52–54} In animal models, SWL has been shown to induce parenchymal injury, which increases with the number of shocks, level of energy, and also with smaller kidneys. Furthermore, SWL is associated with an acute reduction in GFR and renal blood flow due to vasoconstriction.^{55,56} Evaluation of “shocked” kidneys with magnetic resonance imaging, contrast urogram, and nuclear scintigraphy revealed that 74% of patients had abnormal findings after SWL consistent with a renal contusion. However, a long-term effect of SWL on kidney function has not been definitively demonstrated. Eassa and colleagues⁵⁷ found no change in eGFR or in the relative differential renal function of the treated kidney using nuclear scintigraphy at approximately 4 years of follow-up. Even longer follow-up studies suggest that the risk for an elevated SCr level is not increased with SWL compared with PCNL or conservative management.⁵⁸ HTN has been described as a possible long-term complication of SWL in some^{59–61} but not all^{57,62,63} trials. A

recent population-based study did not find an increased risk, suggesting that this complication rarely affects stone formers following SWL.⁶⁴ Pretreatment with low-energy shockwaves followed by a ramp-up protocol in energy seems to be protective against renal injury.⁶⁵ Recently, el-Assmy and colleagues⁶⁶ retrospectively evaluated the long-term effects of SWL in subjects with solitary kidneys with a mean follow-up of 3.8 years and found no significant difference in SCr, systolic and diastolic blood pressure, new onset HTN, calculated GFR, and kidney morphology before and after treatment.

SWL success is dependent of several factors. Stone-free rate (SFR) is influenced by stone size,^{67–70} location,^{71–74} symptom duration previous to the procedure,^{71–74} presence of ureteral stent,^{67,68} gender,⁷⁰ stone density (Hounsfield Units), skin-to-stone distance, and stone composition.^{70,75} The influence of renal function on success rates after SWL, however, is debatable. Lee and colleagues⁷⁶ reported a significantly lower SFR of 57% for subjects with preoperative SCr between 2.0 and 2.9 mg/dL compared with 66% if SCr was less than 2.0 mg/dL ($P < .05$). Hung and colleagues⁷⁰ reported that subjects with proximal ureteral calculi had SFR of only 50% if they had underlying CKD, compared with 93% for subjects with an eGFR greater than 60 mL/min/1.73 m². On multivariate logistic regression analysis, factors negatively affecting SFR were gender (females), eGFR less than 60 mL/min/1.73 m², and stone width greater than 7 mm. Conversely, other studies have failed to find an association between SWL outcomes and preoperative impaired renal function.^{77,78}

PCNL

There have been some attempts to identify predictors of prognosis and outcomes for patients with CKD who have upper urinary tract calculi.^{79,80} Paryani and Ather⁷⁹ retrospectively reviewed 500 subjects with urolithiasis (40% with complete or partial staghorn calculi) and reported that in the 12% with baseline renal insufficiency, most had improvements in function independent of relief of obstruction. Singh and colleagues⁸⁰ prospectively followed 70 subjects with CKD (mean preoperative SCr of 4.76 mg/dL) who underwent PCNL for staghorn or calyceal stones. They reported an average decrease in SCr of 1.53 mg/dL (32%) and an average functional improvement by renal dynamic scans of 20% 9 months postoperative.

Agrawal and colleagues⁸¹ published their experience with PCNL in 78 subjects with calculous nephropathy and advanced renal failure. An

improvement in renal function was seen in most (82%) subjects, whereas in 11 subjects it remained unaltered or deteriorated. Nevertheless, in their study baseline renal function evaluation was performed at presentation, instead of after placing a percutaneous nephrostomy tube or treating any UTI to rule out an overlying component of acute renal failure. They reported parenchymal thickness greater than or equal to 7 mm, clear urine in the collecting system, absence of urosepsis, and recent onset azotemia were predictors of renal recovery. Kukreja and colleagues⁸² reviewed the impact of PCNL on renal function in 84 CKD subjects with renal stones. Subjects with acute rise in creatinine due to obstruction or infection were excluded from the study, but SCr, instead of eGFR, was used to evaluate renal function. They reported an overall improvement in renal function in 33 subjects (39%), stable function in 24 (29%), and decreased function in 27 (32%) with a mean follow-up of 2.2 years. Factors predicting deterioration in renal function were proteinuria greater than 300 mg/d, atrophic cortex less than 5 mm, recurrent UTI, stone burden greater than 1500 mm², time elapsed after PCNL surgery less than 15 years, and finally pediatric age group. In a retrospective study by Canes and colleagues,⁸³ the impact of PCNL on renal function was evaluated in 81 subjects with a solitary kidney. Mean eGFR increased from 44.9 mL/min/1.73 m² preoperatively to 51.5 mL/min/1.73 m² 1 year after intervention. In another large series, Bilen and colleagues⁵¹ evaluated 185 subjects with eGFR less than 60 mL/min/1.73 m² undergoing PCNL and found the mean preoperative eGFR significantly increased from 42.4 to 48.4 mL/min/1.73 m² at three months follow-up. None of the subjects required dialysis during that relatively shorter follow-up. They also found that nearly all subjects with stage 5 CKD had some benefit from surgery, whereas half of stage 4 subjects and only 25% of stage 3 subjects improved. Renal function improvement was the greatest in stage 5 and the least in stage 2 subjects. They hypothesized that the impact of the calculi itself in a severely compromised kidney is greater than the impact of PCNL and the opposite is probably true for moderately affected kidneys in which the harm of PCNL may be more significant, particularly if associated with UTI.

Kurien and colleagues⁸⁴ studied 91 adult subjects with SCr greater than 1.5 mg/dL who underwent PCNL. Most subjects had stage 3 or 4 CKD and most showed improvement or stabilization in renal function after PCNL. Postoperative complications and peak eGFR were the main factors predicting deterioration of kidney function during follow-up.

Similarly, Akman and colleagues⁸⁵ followed 177 subjects who underwent PCNL and had preoperative GFR less than 60 mL/min/1.73 m² for at least 1 year and found a significant improvement in eGFR after a mean 43-month follow-up.

Another important factor that has been proposed to affect renal function in patients with CKD is the number of tracts. Animal studies have shown that PCNL tracts were associated with minimal scar tissue and no significant morphologic or functional alterations.^{86,87} Handa and colleagues⁸⁶ also evaluated the impact of multiple-tract PCNL in pigs and found no significant difference in renal function loss compared with single-tract PCNL. Human studies revealed that renal damage from nephrostomy tracts is minimal based on nuclear renography and has no effect on systemic renal function.^{88,89} Akman and colleagues⁸⁵ series compared 142 subjects treated with one access to 35 subjects with multiple-tract PCNL and found similar renal function among them, even when considering CKD subjects.

SFR after PCNL for patients with CKD depend on imaging modality to define it and timing of the examination itself. Bilen and colleagues⁵¹ reported complete stone-free status on postoperative radiograph of 81.1% in subjects with CKD undergoing PCNL. Clinically significant residual stones (>5 mm) were present in 21 renal units (10.7%) and insignificant residual fragments were seen in the remaining 16 (8.1%). Overall, 5 renal units underwent adjuvant SWL, 10 had second-look PCNL, and 5 underwent ureteroscopy. Kurien and colleagues⁸⁴ defined complete clearance as nonvisualization of residual fragments on radiograph and ultrasonography at 1 month after PCNL. Stone-free status was achieved in 98 renal units (83.7%) with a mean of 1.3 stages per renal unit. SWL as an auxiliary procedure was required for clearance of residual stones in 2.5%. Akman and colleagues⁸⁵ reported SFR at postoperative month 3 of 80.2% (142 out of 177). Definition was based on radiograph, ultrasound, and/or CT. Stone recurred during long-term follow-up in 25.3% of these subjects.

PCNL remains the primary modality for treating complex stones in patients with CKD. However, it is not without complications and the most common are hypothermia, bleeding, metabolic acidosis, serum electrolytes disturbances, urosepsis, and rarely death.^{90,91} Overall PCNL complication rate is 13% to 35% and bleeding remains the leading problem.⁸¹⁻⁸⁵ Anemia and underlying platelet dysfunction in patients with CKD may play an important role in the high rate of transfusion. Bilen and colleagues⁵¹ reported that 38% of CKD subjects had anemia preoperatively and

that blood transfusion rates were as high as 36%. Kurien and colleagues⁸⁴ and Akman and colleagues⁸⁵ had a lower, but still significant, transfusion rate of 20.5% and 9.6%, respectively. Efforts to reduce hemorrhagic complications include ultrasound-guided access, balloon-tract dilatation, optimization of operating time, and staging procedures in cases of large stone burden.⁹²

Despite prophylactic antibiotics, urosepsis remains a major concern, even in patients with CKD who have sterile preoperative urine cultures. Because of the inhibition of cell-mediated immunity and humoral defense mechanisms, sepsis may easily develop in patients with CKD. Agrawal and colleagues⁸¹ reported septic complications in eight of the 78 subjects, out of whom three died (3.8%) despite intensive care. Bilen and colleagues⁵¹ reported septic shock in three subjects, regardless of appropriate antibiotic treatment. Only one subject survived and the overall mortality rate was 1.1%. Kurien and colleagues⁸⁴ reported UTI, defined as culture proven or prolonged febrile episodes, in nine subjects (7.7%) of their series. There were two postoperative deaths and one related septic shock. In the series of Akman and colleagues,⁸⁵ urosepsis was detected in five subjects (2.8%) who were successfully treated with intravenous broad-spectrum antibiotics. No deaths occurred. Steps used in attempts to avoid postoperative infection include adequate preoperative collecting system drainage and preemptive administration of broad-spectrum antibiotics. During the procedure, the use of a large caliber Amplatz sheath to maintain low intrarenal pressure may decrease the incidence of bacteremia in patients with infected stones.^{93,94} Importantly, complete stone clearance is essential to remove all foci of infection. Furthermore, adequate postoperative drainage through a nephrostomy tube or a ureteral stent may reduce bacterial load in the pelvicalyceal system, decreasing the chance of bacteremia.^{95,96} Efforts should also be spent to reduce hospital-acquired infections.

NEPHROLITHIASIS AND QOL

Overview

There are very few studies in regard to urolithiasis that investigate the impact of the disease process, treatment (both medical and surgical) and implementation of lifestyle modifications on the QOL of patients. Most studies look at SFR as an endpoint for effective management. Looking at the nature of the disease, a patient often is diagnosed with urolithiasis due to the onset of debilitating flank pain. Intervention may or may not be indicated.

The patients are often asked to change their diet or begin medications to lower stone recurrence rates. All of these associations, in addition to the high recurrence rates, can have a significant impact on the QOL of a patient.

Stone formers have been shown to have more stressful life events. There have even been links to renal colic and symptoms of anxiety and depression. Furthermore, interventions for urolithiasis can also have an effect on QOL. Ureteral stents, PCNL, URS, and SWL all have their own associated side effects and complications that can affect outcomes in regard to patient well-being beyond SFR.

The following is a comprehensive look at the literature and compilation of a review of the effects of urolithiasis on patient QOL. Associations between stone disease and stress and/or psychiatric disorders and how interventions (surgical and medical) may affect patient QOL are discussed.

Stress, Depression, and QOL in Patients with Urolithiasis

Negative emotional and psychological effects of chronic disease can be seen in stone formers. Like other chronic diseases, there have been associations between urolithiasis and stress, depression, and further psychological disorders. Stress is a psychological term related to the perception of one's mental and physical well-being. It is not clear whether stress is a cause or an effect of a given condition or situation. Either way, patients experience a change in their perception of their own well-being and sometimes have physiologic reactions to these stressors. It is well known that chronic diseases are associated with increased stress levels.

When compared with the general population, recurrent stone formers and those with other chronic diseases have higher stress levels. In stone formers, increased stress has been associated with presence of symptoms.⁹⁷ It has been shown in case control studies that stressful life events were significantly greater in patients with recurrent painful renal colic.⁹⁸ When comparing validated stress questionnaires, Miyaoka and colleagues⁹⁷ have shown increased stress levels in those with the presence of symptoms but no significant difference in stress between recurrent stone formers and nonrecurrent stone formers. One might infer from this data that acute exacerbations of chronic illness cause increased stress levels, and the presence of symptoms (ie, renal colic) is the true stressor independent of chronicity of disease.

Najem and colleagues⁹⁹ have shown an increase in incidence of symptomatic stone disease in subjects who have preceding stressful life events. The notion of stress causing renal calculi has been proposed, but difficult to prove. Onset of stress can easily be determined from good history taking and the timing of stressful life events such as loss of employment, death of a loved one, or other traumatic event. However, it is difficult to determine the onset of calculi formation in relation to the timing of the stressor. Because all stones must start from a nidus and are initially asymptomatic, it proves difficult to determine if stone formation precedes the stressor (ie, the effect model of stress) or if the stressor actually predates the calculi formation (ie, the cause model of stress).^{97,99}

Depression has also been linked to chronic diseases, and it is no surprise that there is a higher prevalence of reported depression in patients with urolithiasis. In the United States, depression has a lifetime prevalence of 16.5%.¹⁰⁰ Diagnosis of depression is defined by the *Diagnostic and Statistical Manual of Mental Disorders (DSM) IV* criteria. Patients must exhibit depressed mood and/or decreased functionality in addition to five or more of the following: weight loss or weight gain, insomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness, decreased ability to think or concentrate, or recurrent thought of death or suicidal ideation.¹⁰⁰

A key characteristic for clinically diagnosed depression is that the *DSM IV* criteria cannot be caused by an underlying medical condition.¹⁰¹ When assessing chronic diseases like urolithiasis, it is important to determine if the *DSM IV* criteria are caused by associated symptoms of stone disease. When looking at increased depression rates in chronic diseases, such as chronic obstructive pulmonary disease, asthma, diabetes, and congestive heart failure, one can postulate that the depressive symptoms exist during and well after acute exacerbations of the underlying chronic disease. However, there have not been many studies looking at clinically diagnosed depression and urolithiasis. Angell and colleagues¹⁰² reported a correlation between depression and urolithiasis; however, this study used a depression symptom questionnaire and did not clinically diagnose depression as defined by the *DSM IV*. Patients with a stone episode within the past year and those requiring greater than one emergency room visit had a "significant level of physiologic distress" according to their scores on the depression questionnaire. A study from Taiwan reported that subjects with newly diagnosed urinary calculi are 1.75 times more

likely to be diagnosed with depressive disorder within 1 year than controls.¹⁰³ Diniz and colleagues¹⁰⁴ have shown a significant linear correlation between symptoms of depression and the number of recurrent renal colic episodes. As shown in other illnesses with pain exacerbations, there is a reciprocal correlation between pain and depressive symptoms. For example, individuals with chronic lower back pain are more likely to have depressive symptoms after 2 years, and patients with baseline depressive symptoms are more likely to experience debilitating lower back pain exacerbations.¹⁰⁵

Researchers have started to look at overall QOL in regard to patients with chronic urolithiasis. Instead of looking at stress and depression as individual symptoms, QOL questionnaires can encompass a variety of symptoms and give investigators a better understanding of how chronic urolithiasis affects patients' perception of their own mental and physical well-being. There have been many studies looking at urolithiasis and health-related QOL outcomes. Similar to stress and depressive symptom studies, QOL investigations assess patient well-being in relation to renal colic symptoms, chronicity of disease, and urolithiasis interventions. QOL studies may provide better insight (compared with stress and depressive studies) into how recurrent stone formers perceive their own health and may potentially influence management and treatment outcomes with overall patient well-being taken into consideration.

QOL is usually determined via a questionnaire or survey. Based on scores, the QOL of patients with urolithiasis can be compared with the general population. The most commonly used QOL questionnaire for urolithiasis in the literature is the SF-36 (Short Form-36) health survey, a validated 36 item general health and well-being questionnaire split into domains encompassing physical, social, and emotional health. In total there are eight domains: physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.

Similar to increased stress and depression symptoms, patients with recurrent symptomatic urolithiasis have a decreased QOL. In case control studies, subjects with recurrent painful renal colic have a substantially impaired QOL.¹⁰⁶ Patients with a stone episode less than 1 month before surveying also have lower QOL scores; however, as seen with stress and depression indices, people with remote stone episodes have comparable QOL scores to those of the general public.¹⁰⁷ Within groups of patients with urolithiasis, patients with comorbid conditions such as obesity, HTN, and diabetes tend to have worse QOL scores

than their associated counterparts.^{107,108} Female stone formers also tend to have a lower QOL compared with their male counterparts.¹⁰⁸ Universal among studies comparing stone formers' QOL with the general population show that all domains are not uniformly lower in stone formers. Penniston and Nakada¹⁰⁸ found statistically significant differences in stone formers in the bodily pain and general health domains only. Bensalah and colleagues¹⁰⁷ found lower scores in five of eight domains (physical functioning, role-physical, general health, role-emotional, and social functioning) in their stone formers compared with the US general population. Bryant and colleagues¹⁰⁹ found decreased QOL scores in six of eight domains (physical function, role physical, bodily pain, general health, vitality, and social function) in their stone former population. They reported lower QOL in patients with recent stone events, greater than one emergency room visit, and in those with greater than two surgical procedures.

Discrepancies in QOL scores between populations of stone formers at different institutions are evident when reviewing the literature. Donnelly and colleagues¹¹⁰ looked at these discrepancies by questioning the validity of the SF-36 QOL questionnaire in subjects with urolithiasis. When comparing QOL after a recent stone event to those 18 months later with no recurrence, there were no differences in QOL scores. One would anticipate that an improvement in disease and an absence of symptomatic recurrence would show an improvement in QOL scores. By definition, in order for a QOL questionnaire to be validated for a specific disease, there must be improvements in scores when there are improvements in the disease on follow-up survey.

Importantly, 20 of the 36 questions in the SF-36 questionnaire are specific to events within the last 4 weeks. This could be why recent symptomatic stone events correlate to significantly lower QOL scores. Score and domain discrepancies in the QOL questionnaire between populations of recurrent stone formers at different institutions can in part be attributed to the natural progression of recurrent stone formation and the timing bias seen in the SF-36 questionnaire.

Management of Urolithiasis and QOL

In addition to QOL evaluation for urolithiasis and its associated symptoms, it is also important to evaluate QOL in regard to management of urinary stone disease. Urolithiasis has multiple treatment modalities. Over the years, treatment of kidney stones has become less invasive and there has

been broader adoption of medical management and dietary modifications to prevent recurrence. Historically, endpoints of clinical studies have been SFR, which are defined by nonstandardized postmanagement imaging. Patients are counseled on which intervention and/or management strategy would achieve optimal SFR. QOL is not usually addressed with the proper attention.

The European Association of Urology (EAU) and American Urological Association (AUA) have established treatment guidelines for urolithiasis based mainly on stone size, location, and density (EAU/AUA Guidelines, 2005–2008). Most of these recommendations were tailored based on trials' SFR and even within guidelines there are still some areas of uncertainty, including management of asymptomatic renal stones, lower pole calculi, and small ureteral calculi. Urologists may propose multiple surgical interventions as options to their patients if a definitive treatment modality has not yet been proved superior. Overall, there are few clinical trials prospectively comparing different surgical management options for urolithiasis with QOL incorporated as an endpoint.

Keeley and Assimos¹¹¹ and Keeley and colleagues¹¹² showed that, in subjects with asymptomatic renal calculi, SWL had a reduced need for surgical intervention after a 2-year follow-up compared with observation. However, there was no difference in QOL or SFR between the two groups. When reviewing the literature on lower pole calculi, SFR are higher in subjects receiving PCNL and URS compared with SWL.^{111–114} Clinically, SWL is not as effective for lower pole calculi but, when looking at QOL outcomes, patients who underwent SWL compared with URS had fewer complications, required less pain relief, and were more likely to choose SWL again.^{111,113} According to Albala and colleagues,¹¹⁴ when compared with PCNL for lower pole calculi, SWL had similar SF-36 scores, indicating no difference in QOL outcomes. Again, the PCNL group had a higher SFR, but had more complications. When comparing PCNL to URS for lower pole stones, higher SFR and a reduced need for secondary procedures were seen in the PCNL group, but a similar QOL score was found among cohorts. Even though the PCNL group had more complications, when questioned, more subjects would prefer PCNL again in comparison to URS for management of their lower pole calculi.¹¹¹ When looking at ureteral calculi, URS achieves higher SFRs and a reduced need for repeat intervention when compared with SWL.¹¹⁵ However, URS is associated with a higher complication rate and increased hospital stay, both of which can affect QOL outcomes.

In addition to the above-mentioned controversies, disagreement also persists concerning ureteral stenting for stone disease. With regard to SFR, stenting versus not stenting for URS is similar.¹¹⁶ Ureteral stenting in combination with SWL or URS may be required but is not without drawbacks that should be addressed during patient counseling. Most individuals will experience one or more known side effects: irritative voiding symptoms, pain, incontinence, and/or hematuria. Joshi and colleagues^{117,118} looked at QOL issues in subjects with ureteral stenting and the SF-36 questionnaire was shown to be neither specific nor sensitive in these studies. The investigators developed disease-specific QOL questionnaires, which incorporated general health scores and the described stent-associated symptoms, as well as sexual health complications. It was determined by using these validated disease-specific questionnaires that ureteral stenting is associated with significant morbidity and reduced QOL in 80% of patients with stents. These results strongly reinforce the need for QOL measures to be considered when determining management of urolithiasis. Based on the studies of Joshi and colleagues,^{117,118} it becomes clear that a critical evaluation of indications for ureteral stenting after uncomplicated urolithiasis procedures is required to identify those patients who will benefit from temporary diversion.

Strong efforts have been made in the basic science and clinical research arenas to better understand the pathophysiology of stone disease and to prevent recurrent stone disease. Nevertheless, half of patients have repeated stone episodes after their initial event regardless of initial intervention.^{119,120} Evidence shows that increasing fluid intake can greatly reduce the risk of repeat stone formation, regardless of the type of calculi. Meta-analysis through systematic review of randomized controlled trials by Fink and colleagues¹²¹ established the efficacy of fluid intake modification by showing that high water intake lowered the long-term risk of nephrolithiasis recurrence by 60%. The efficacy of dietary modification is less understood, but low animal protein diets, and decreased sodium and oxalate intake have been shown to decrease stone recurrence rates.^{120–122} As more is understood about metabolic abnormalities in recurrent stone formers, targeted medical therapy is being investigated to reduce repeat stone episodes. Potassium citrate can reduce stone formation rates by greater than 90% in patients with hypocitraturia.¹²³

Despite the abundant data supporting dietary modifications and long-term medication use for reducing stone recurrence, to the authors knowledge

there are no evaluations correlating dietary modifications and long-term medications to patient QOL in stone formers. Both increased fluid intake and chronic medication use can have compliance issues and dramatically affect ones QOL. For example, some patients' daily lives may not be very accommodating to the frequent restroom breaks which are associated with increased fluid intake, including health professionals, teachers, and truck drivers. Furthermore, it may be unfair to compare chronic medication use in other diseases that may lead to life-threatening sequelae (eg, diabetes, HTN) with the need for chronic medication for stone formers. Each medication has specific side-effect profiles to consider that may affect QOL and compliance. To address this, new formularies, such as Urocit-K 15, are being developed to allow increased dosing flexibility, improved compliance, and better tolerability.¹²⁰ Drug companies and physicians should continue to strive for improved treatment regimens that emphasize patient compliance and tolerability in hopes that this improves QOL.

SUMMARY

Although stone research has lead to evolution in the understanding of stone pathophysiology, revolution in approaches to stone prevention, and innovation in surgical management of calculi, the next step is a critical assessment of the impact of these advancements on patients' QOL and CKD. Physicians should strive to treat the disease and the patient, with an eye on optimizing patient well-being. For a generally non-life-threatening disease such as urolithiasis, QOL outcomes and impact on renal function must be taken into consideration.

Initial studies using the SF-36 questionnaire have been promising in determining patients' perception of their own well-being in regards to stone disease management. However, the evident discrepancies in SF-36 results among different populations at various institutions warrant critique of this generalized questionnaire. Validated urolithiasis-specific QOL questionnaires are needed. By combining a stone-specific questionnaire with the SF-36, some investigators were able to better correlate certain stone specific variables with lower QOL scores.¹⁰⁹ With a validated urolithiasis QOL questionnaire, appropriate interventions and proper management to prevent recurrence can be evaluated beyond the objective scope of stone-free and reduced recurrence rates. Validated questionnaires, such as the SHIM (sexual health inventory for men) score and AUA-SS (American Urological Association Symptom Score), have been used in the management and

treatment of other urologic diseases, such as erectile dysfunction and lower urinary tract pathologic states, and it is time for the same caliber of validated questionnaire for the treatment and management of stone disease.

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Rianne J.M. Lammers, Richard J. Sylvester, Cheryl T. Lee, and J. Alfred Witjes

The natural history of non-muscle invasive bladder cancer (NMIBC) in individual patients can be unpredictable. Although there are known clinical and molecular factors associated with tumor recurrence and progression, it is challenging to reconcile these data during a typical patient encounter within a busy clinic. The authors discuss the European Organization for Research and Treatment of Cancer's risk tables along with other models for predicting prognosis in patients with NMIBC. The authors also describe their advantages and disadvantages and the barriers to using these risk models in daily clinical practice and provide a future perspective on prognostic models.

Urinary Markers/Cytology: What and When Should a Urologist Use	165
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Jeffrey M. Tomasini and Badrinath R. Konety

As of 2012, bladder cancer is the fourth most common cancer afflicting men and ninth most common cancer in women. Nearly 80% of all bladder cancer diagnoses are non-muscle invasive at presentation, most of whom will develop recurrent disease within 5 years of initial diagnosis. Urinary tumor markers provide a noninvasive method for both screening and surveillance of bladder cancer. This article reviews the current Food and Drug Administration–approved urinary biomarkers for detection of non-muscle invasive bladder cancer.

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Brock B. O'Neil and William T. Lowrance

This article summarizes the current literature on office-based management of low-grade, noninvasive bladder cancer. Discussion includes differences in recurrence and progression rates between neoplasm grades and stages, role of visual grading for diagnosis, cost advantages of treatment outside the operating room, and a step-by-step description of office-based procedures.

Perioperative Chemotherapy: When to Use It, What to Use, and Why	183
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David C. Johnson, Raj S. Pruthi, and Michael E. Woods

This article provides an overview of intravesical chemotherapy agents used for non-muscle invasive bladder cancer; summarizes the evidence on single-dose

perioperative administration, induction therapy, and maintenance therapy; and briefly discusses ongoing research.

Side Effects of Perioperative Intravesical Treatment and Treatment Strategies for These Side Effects

197

Joshua G. Griffin and Jeff Holzbeierlein

Perioperative intravesical chemotherapy has a well-established role in the treatment of non-muscle invasive bladder cancer. There are multiple agents that can be used in this fashion with varying properties. Although chemical cystitis is the most common side effect and is usually self-limiting, significant toxicity can occur with intravesical chemotherapy. It is imperative that the urologist is aware of the acute and delayed side effects of intravesical chemotherapy and how to manage potential complications. Both local and systemic toxicities are discussed, as well as strategies to minimize and manage them.

Strategies for Optimizing Bacillus Calmette-Guérin

211

Jay B. Shah and Ashish M. Kamat

For treating patients with superficial bladder cancer and a moderate-to-high risk of tumor recurrence or progression, intravesical BCG has been the key development of the last generation. However, BCG has also brought with it a novel set of challenges. An understanding of when, to whom, and how BCG should be given is critical if optimal outcomes are to be achieved. This article the authors reviews the role that BCG has played in the management of bladder cancer over the last several decades and discusses specific approaches to optimize BCG. It focuses on selection and technical strategies.

New Agents for Bacillus Calmette-Guérin—Refractory Bladder Cancer

219

Jennifer J. Ahn and James M. McKiernan

Bacillus Calmette-Guérin has been established as the primary treatment of high-risk non-muscle invasive bladder cancer. If patients do not respond or later recur, the most reliable treatment option is cystectomy. For those who are unwilling or unable to undergo this significant procedure, there is a multitude of alternative intravesical therapies. This article provides an overview of treatment options for patients with non-muscle invasive bladder cancer who have failed intravesical bacillus Calmette-Guérin therapy. It includes information on recent and ongoing trials and serves as a guide for clinicians regarding available therapies and a reference for researchers in this field.

Determining the Role of Cystectomy for High-grade T1 Urothelial Carcinoma

233

Siamak Daneshmand

High-grade T1 (HGT1) urothelial carcinoma is an invasive disease with high predisposition for recurrence and progression. The optimal treatment of HGT1 disease remains controversial. Clinical HGT1 disease represents a heterogeneous group of patients with variable clinical behavior. Radical cystectomy for HGT1 disease is associated with excellent survival and offers the best opportunity for cure; however, it has a potential cost of decrease in quality of life. This article summarizes features associated with increased risk of progression and provides a framework for optimal treatment strategy with a focus on the role of radical cystectomy for HGT1 disease.

The Conundrum of Prostatic Urethral Involvement 249

Johann P. Ingimarsson and John D. Seigne

The presence and depth of urothelial cancer involvement in the prostatic urethra can significantly affect the management of a patient with non-muscle invasive bladder cancer. This article presents an overview of the incidence, diagnosis, management, and follow-up of urothelial cancer.

The Costs of Non-Muscle Invasive Bladder Cancer 261

Andrew C. James and John L. Gore

Bladder cancer is a common diagnosis, affecting 70,000 Americans each year. Because the diagnosis, management, and long-term follow-up of non-muscle invasive bladder cancer requires advanced imaging and invasive testing, economic evaluations have shown bladder cancer to be the costliest cancer to treat in the US on a per capita basis. Adjunctive tests for surveillance have not obviated the need for cystoscopy and cytology. Indirect costs to patients include loss of work, decreased productivity, and diminished quality of life associated with diagnosis, treatment, and surveillance. Improved value may be achieved with better compliance with evidence-based practices for non-muscle invasive bladder cancer care.

New Imaging Techniques for Non-Muscle Invasive Bladder Cancer: Ready for Primetime 271

Joseph A. Gillespie and Michael A. O'Donnell

Treatment of non-muscle invasive bladder cancer (NMIBC) requires direct visual appreciation of the tumor. Transurethral resection that is dependent solely on white light cystoscopy (WLC) often fails to accurately stage or completely resect NMIBC. These deficiencies of WLC are significant contributors to the high rates of recurrence and eventual progression to muscle invasive disease. This article looks at technologies that are being used in adjunct to WLC to augment the urologist's ability to identify, stage, and treat NMIBC.

Diagnostically Challenging Cases: What are Atypia and Dysplasia? 281

Joseph Sanfrancesco, J. Stephen Jones, and Donna E. Hansel

This article addresses the spectrum of atypia and dysplasia within the bladder epithelium and the diagnostic categories developed to further classify challenging lesions. In addition, the effects of inflammation, specific therapies, and instrumentation on the bladder mucosa as well as the associated difficulty in achieving the appropriate diagnosis are also discussed.

Restaging Transurethral Resection for Non-Muscle Invasive Bladder Cancer: Who, Why, When, and How? 295

Chad R. Ritch, Peter E. Clark, and Todd M. Morgan

The rate of clinical understaging in non-muscle invasive bladder cancer (NMIBC) after an initial transurethral resection (TUR) is significant, particularly for high-grade disease, and this has a major impact on prognosis. A repeat TUR, 2 to 6 weeks following the initial resection, is recommended in appropriately selected cases to avoid diagnostic inaccuracy and improve treatment allocation. This article summarizes the rationale and indications for performing a repeat TUR in NMIBC and also provides information regarding patient selection and technique.

Optimal Risk-Adapted Surveillance Strategies for NMIBC, Including Upper Tract Imaging 305

Michael C. Large, Joshua A. Cohn, and Gary D. Steinberg

Non-muscle invasive bladder cancer (NMIBC) represents approximately 70% of all incident cases of bladder cancer. The financial burden of NMIBC continues to increase, underscoring the importance of efficient, evidence-based management of this disease. Consensus guidelines differ on risk definition and in management recommendations. This article reviews the incidence and financial impact of NMIBC and details the recommendations for diagnosis, treatment, and surveillance made by the American Urological Association, International Consultation on Bladder Cancer-European Association of Urology, and National Comprehensive Cancer Network. Established and developing adjunctive laboratory and imaging tests directed at diagnosis and management of NMIBC are also discussed.

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PROGRAM OBJECTIVE:

The goal of *Urologic Clinics of North America* is to keep practicing urologists and urology residents up to date with current clinical practice in urology by providing timely articles reviewing the state of the art in patient care.

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Practicing urologists, urology residents and other health care professionals practicing in the discipline of urology.

LEARNING OBJECTIVES

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- Recognize the role of cystectomy for high grade T1 urothelial carcinoma.
- Review side effects of perioperative intravesical treatment.

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Preface

Non-Muscle Invasive Bladder Cancer



Sam S. Chang, MD, FACS
Editor

As the second most frequent genitourinary malignancy, non-muscle invasive bladder represents a significant, heterogeneous disease that urologists commonly diagnose, evaluate, and treat. The range of this disease process from an innocuous single, small papillary tumor to multiple T1 bladder tumors is impressive. Overtreatment and undertreatment are considerations for each of us as we attempt to individualize and optimize our care. Ever present as well are patient quality-of-life concerns and the economic health cost burden.

Over the past decade new discoveries have improved diagnosis and management of this disease, but despite these, we still follow certain practice patterns based only on historical precedent. There is much we need to learn and much we need to research. Herein, leaders in this field contribute

articles focusing on specific areas of controversy and need. The reader will find up-to-date information on cancer diagnosis, evaluation, and treatment that includes practical solutions to difficult clinical situations.

I hope you learn as much as I have from this volume.

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Foreword



Samir S. Taneja, MD
Consulting Editor

Non-muscle invasive bladder cancer (NMIBC) represents, in effect, a constellation of diseases. Among cancers labeled as “non-muscle invasive” are those with virtually benign behavior and those with a highly lethal phenotype. As such, the management has evolved greatly in the past 30 years, and the current “state of the art” reflects one of the most well-developed risk-stratification schemes in urologic cancers. Identification of high-risk disease leads to a completely different treatment paradigm than that carried out in the remaining patients.

The prevalence of the NMIBC, along with the high rate of recurrence, makes it a disease with tremendous financial implications in the upcoming era of health care reform. Proper, evidence-based management has the potential to not only improve patient outcome but also reduce overall costs associated with the care of these patients. This will secondarily influence the allocation of dollars to urologic disease overall.

Although there are now a number of national and international guidelines published regarding the management of NMIBC, the entire story of how to manage these patients is far from written. Ongoing controversies in risk stratification, timing of therapy, and sequence of therapy continue

to fuel controversy. I am deeply indebted to Dr Sam Chang for his willingness to serve as guest editor for this issue of the *Urologic Clinics* and to put much of the ongoing controversy into a cohesive framework. He has solicited articles from the brightest and best in formulating this fantastic issue. In keeping with our ongoing effort to provide a multidisciplinary perspective on urologic disease, the articles in this issue cover a range of topics including both the management of NMIBC and the impact of the disease itself on Urology. I am confident that this issue will both educate you regarding the management of your patients and challenge you to explore the ongoing controversies.

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NMIBC Risk Calculators

How Useful Are They for the Practicing Urologist and How Can Their Clinical Utility Be Improved?

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KEYWORDS

• Non-muscle invasive bladder cancer • EORTC • Risk table • Prognostic model

KEY POINTS

- The natural history of non-muscle invasive bladder cancer in individual patients can be unpredictable.
- Although there are known clinical and molecular factors associated with tumor recurrence and progression, it is challenging to reconcile these data during a typical patient encounter within a busy clinic.
- Prognostic models, such as risk tables and nomograms, aim to facilitate risk stratification, patient counseling, and treatment decision making.
- There are many prognostic models available for non-muscle invasive bladder cancer, but they are not commonly used in daily practice because of their complexity and limited usefulness in treatment decision making.
- To make prognostic models more useful, the focus should be on the clinical implications of the model for the patient, such as by focusing on negative and positive predictive value, rather than *P* values, sensitivity, and specificity. The net benefit of the model should be compared with the standard model by means of classification tables and decision analytic techniques to test its additional clinical value.
- Biomarkers do not have sufficient additional value, and markers undergoing investigation should first stand the test of time.
- Ultimately, even good models will not be translated into clinical practice unless they can be integrated into the standard clinical workflow.

BACKGROUND

Overall, bladder cancer (BC) is the seventh most common malignancy in men and the 17th in women.¹ The incidence increases with age and is

highest at 50 to 70 years of age. Eighty percent of patients with BC are men.² Important risk factors are chemical and environmental exposures, such as smoking and aromatic amines, and chronic irritation.^{3,4} In the Western world,

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more than 90% of BC are urothelial carcinomas or transitional cell carcinoma.⁵

On average, 70% of patients with BC present with non-muscle invasive BC (NMIBC) and the remainder with muscle-invasive disease (MIBC). In the non-muscle invasive group, approximately 70% present as Ta lesions (noninvasive papillary carcinoma), 20% as T1 lesions (invasion into subepithelial connective tissue), and 10% as carcinoma in situ (CIS or Tis lesions; high-grade noninvasive flat tumor).⁶ For grading, both the World Health Organization's (WHO) 1973 and the WHO's 2004 classifications are advised. The WHO's 1973 grading system recognizes 3 groups: grade 1 to 3. The WHO's 2004 classification defines 4 groups of papillary lesions: urothelial papilloma (benign), papillary urothelial neoplasm of low malignant potential, low-grade papillary urothelial carcinoma, and high-grade papillary urothelial carcinoma.⁷ For staging, the TNM classification is used.⁸

Another way to stratify patients is by prognostic factors and, thus, outcome. The European Organization for Research and Treatment of Cancer (EORTC) developed a prognostic model for recurrence and progression for patients with NMIBC,⁹ which the authors discuss in this article. Other prognostic models with applications in urological practice have been created recently using other techniques: nomograms, neuro-fuzzy models, and artificial neural networks (ANN).

The most well-known prognostic model is the risk table, which divides patients into risk groups based on their score. It gives the probability of an event (recurrence, progression) for patients within a given risk group. It assumes that all patients within a given risk group have a similar prognosis; however, the choice of cutoff values when stratifying patients into groups is somewhat artificial. It is unlikely that all patients within a given group will have the same prognosis, and patients with similar scores who fall into different risk groups might not have different prognoses. Furthermore, when one variable is missing, it is not possible to calculate the probabilities. Nevertheless, risk tables can easily identify the very low- and very high-risk patients.

A nomogram is a graphical device that is used to calculate an individual patient's probability of an event based on a multivariable model with their specific prognostic factors and, hence, gives a more individualized risk calculation. Nomograms are based on a (continuous) score, whereas risk tables subdivide patients into different categories based on their score. They provide a more individualized probability of the event of interest, and software is usually developed to make them easy to

use. Because the nomogram probabilities come directly from the multivariable model, it is important that the model is well calibrated, that is, it has an excellent goodness of fit. Otherwise, the probabilities provided by the model will be incorrect. However, when one of the variables is missing for a patient, the nomogram cannot be used for that patient. As mentioned by Hernandez and colleagues,¹⁰ nomograms are usually developed with very large series, and it has to be determined if they are applicable to lower-volume centers.

More advanced prognostic models are neuro-fuzzy models and ANN. The latter is a mathematical model based on a biologic neural network. It can handle complex relationships between input and output and can find patterns in the data. ANN are adaptive systems that can change their structure during the learning phase. A neuro-fuzzy model is a combination of an ANN and fuzzy logistics, which is a form of logistics that can handle reasoning. Because there is little experience in NMIBC with these models, they are not discussed further.

In the next paragraphs, the advantages and disadvantages of the most well-known prognostic model, the EORTC risk tables, are discussed. Then, several other NMIBC prognostic models are described; the authors discuss the lack of use of prognostic models in the daily urological practice. Finally, the authors provide a future perspective on prognostic models: how should we develop and use prognostic models for patients with NMIBC?

EORTC RISK TABLES

Development of the EORTC Risk Tables

In 2006, Sylvester and colleagues⁹ published the EORTC scoring system for NMIBC. They combined individual patient data of 2596 patients from 7 EORTC trials (inclusion period: January 1979–September 1989). The aim was to provide simple tables that would allow urologists to easily calculate the probability of recurrence and progression after transurethral resection of the bladder tumor (TURBT) for patients with NMIBC. The most appropriate adjuvant treatment after TURBT and the frequency of follow-up can then be determined in an individual patient based on their prognosis. Data on patient and tumor characteristics and the endpoints of time to first recurrence and time to progression to MIBC were merged. The most important variables were then determined by regression models. Patients were divided into 4 risk groups for both recurrence and progression according to their total score. Probabilities of recurrence and progression at 1 year

and 5 years were calculated. Also, software was provided to calculate these probabilities at 1, 2, 3, 4, and 5 years. The model accuracy using Harrell's bias corrected concordance index (c index) was calculated. The c index is the probability that for 2 patients chosen at random, the patient who had the actual event first had a higher probability of having the event according to the model; an uninformative model will have a c index of 0.5 or 50% (flipping a coin), and a perfect model will have a c index of 1 or 100%. Area under the curve (AUC) can also provide this information but only for binary outcomes (recurrence yes/no). To adjust for bias (overfitting, overoptimism), models were refit 200 times using the bootstrap technique (internal validation). Bootstrapping is a resampling method in which analyses are repeated many times but with different random samples of subjects each: in each analysis some subjects might not be included, others are included once, twice, and so forth. The 2596 eligible patients had mainly favorable characteristics. A total of 22% received no adjuvant intravesical treatment before recurrence; 78% of the patients received intravesical therapy, mostly chemotherapy. The median follow-up was 3.9 years. In total, 47.8% of patients experienced a recurrence with a median time to recurrence of 2.7 years. The most important factors that influenced the time to first recurrence were prior recurrence rate, number of tumors, and tumor size. Only 10.7% of patients experienced progression to muscle-invasive disease. The median time to progression was not observed, with progression

rates at 5 years varying from 0.8% to 45%. The most important factors influencing time to progression were T category, CIS, and grade. Scores were calculated for each patient, varying from 0 to 17 for recurrence and 0 to 23 for progression. **Table 1** gives an overview of the probabilities of recurrence and progression. Furthermore, Sylvester and colleagues⁹ found that concomitant CIS is the most important prognostic factor in patients with pT1G3-tumors, and that recurrence at first follow-up cystoscopy at three months is associated with a higher chance of progression.

As mentioned in an editorial comment by Karakiewicz, the internal validation yielded a c index of 0.66 for recurrence at both 1 and 5 years, which means that 66% of recurrences were accurately predicted at 1 and 5 years. The c index for progression was 0.74 at 1 year and 0.75 at 5 years.⁹

In 2013, the EORTC will start updating these risk tables for patients treated with maintenance bacillus Calmette-Guerin (BCG).

The NMIBC guidelines panel of the European Association of Urology (EAU) classified patients into subgroups of low, intermediate, and high risk based on these tables (**Table 1**, last column) and provided treatment and follow-up recommendations depending on a patient's risk group.¹¹ The American Urological Association (AUA) also specified therapy based on clinical risk. However, the panel of the AUA defined only 2 risk groups: low-risk patients (pTa, low grade) and high-risk patients (pT1, high grade, and/or CIS).¹²

Table 1
Probability of recurrence and progression according to total score⁹ and classification system by the NMIBC guidelines panel of the European Association of Urology¹¹

Recurrence Score	Probability of Recurrence at 1 y		Probability of Recurrence at 5 y		Recurrence Risk Group
	(%)	(95% CI)	(%)	(95% CI)	
0	15	(10–19)	31	(24–37)	Low risk
1–4	24	(21–26)	46	(42–49)	Intermediate risk
5–9	38	(35–41)	62	(58–65)	Intermediate risk
10–17	61	(55–67)	78	(73–84)	High risk
Progression Score	Probability of Progression at 1 y		Probability of Progression at 5 y		Progression Risk Group
	(%)	(95% CI)	(%)	(95% CI)	
0	0.2	(0–0.7)	0.8	(0–1.7)	Low risk
2–6	1	(0.4–1.6)	6	(5–8)	Intermediate risk
7–13	5	(4–7)	17	(14–20)	High risk
14–23	17	(10–24)	45	(35–55)	High risk

Abbreviation: CI, confidence interval.

Disadvantages

As mentioned earlier, patient and tumor characteristics influence the probability of recurrence and progression. However, it should be taken into account that 22% of patients received no intravesical treatment at all, and the treatment that was given consisted mostly of intravesical chemotherapy. Only 171 of the patients (7%) received BCG and none received BCG maintenance. Also, less than 10% of patients received a single immediate postoperative instillation with chemotherapy, and a re-TURBT was not performed in high-risk patients. As mentioned in the discussion by Sylvester and colleagues,⁹ data for other factors that might be of prognostic importance were not available: depth of lamina propria invasion, location of the tumor on the bladder wall, lymphovascular invasion, and micropapillary tumors. Also, recent developments, such as molecular markers, fluorescence cystoscopy and re-TURBT, that are likely to further reduce the risks of recurrence and progression were not taken into account.¹³ Unfortunately, long-term follow-up is not available in most large series of patients where these new treatment developments and more recently identified prognostic factors have been assessed.

Many of the patients included in the EORTC series, particularly those in the high-risk category, would be undertreated according to today's standards. As such, the recurrence rates and especially the progression rates are likely to be somewhat higher than those found in contemporary practice. Thus, the progression rates and to a lesser extent the recurrence rates published in the EORTC series should be similar to the untreated natural history of the disease, enabling one to determine the most important prognostic factors without having to take into account treatment as a confounding factor. One can, however, ask what the real value of these risk tables is in the treatment decision process because the positive predictive value (PPV) of the EORTC risk table for progression in high-risk patients is low, only 21%. This subject is discussed in more detail later in this article.

External Validation

Several groups have independently validated the EORTC risk tables.^{10,14–18} Fernandez-Gomez and colleagues¹⁸ performed an external validation in 1062 patients with NMIBC treated with maintenance BCG. For recurrence, Fernandez-Gomez and colleagues found a lower risk in each group of patients than Sylvester and colleagues,⁹ but the c index was comparable. For progression, lower risks were found in the cohort from

Fernandez-Gomez and colleagues,¹⁸ especially in the highest-risk group at 5 years. The limitations as discussed by the investigators are the lack of re-TURBT and a short maintenance regimen. The investigators also mention the difference in the distribution of patients: there are more patients with aggressive tumor characteristics in this cohort than in the EORTC cohort. As mentioned in an editorial comment by Sylvester,¹³ application of the EORTC scoring system in the BCG series to predict progression yields a sensitivity of 88% and a negative predictive value (NPV) of 95%, but the PPV is only 17%. PPV is the proportion of positive test results that are true positive; thus, it reflects the probability that a positive test reflects the underlying condition being tested for. NPV is the proportion of subjects with a negative test result who are correctly diagnosed and, thus, without the investigated disease. Overall, this is a well-performed external validation, which shows that although the EORTC risk tables provided an adequate discrimination between patients with a different prognosis, their calibration was poor in patients treated with BCG.

Van Rhijn and colleagues¹⁶ validated the EORTC risk scores in 230 Dutch patients with primary NMIBC. Additionally, they proposed an alternative to pathologic grade with molecular grade (mG) based on fibroblast growth factor receptor 3 (FGFR3) gene mutation and MIB-1 expression. The median follow-up was 8.6 years. In general, 5-year recurrence-free survival (RFS) and progression-free survival (PFS) rates were lower in the cohort of Van Rhijn and colleagues than in the EORTC-cohort. According to the authors, the differences in PFS may be explained by the lower number of patients, by the selection of only primary patients, by the longer median follow-up, or because 32% of patients died of other causes. Furthermore, they found that mG was related to progression and disease-specific survival, and adding mG increased the predictive accuracy for progression from 74.9% to 81.7%. These data suggest a potential advantage to incorporating molecular markers into the EORTC risk score.

Sakano and colleagues¹⁴ validated the EORTC risk group stratification in 529 Japanese patients with NMIBC. The investigators concluded that the risk stratification as mentioned in the EAU's guidelines is probably not applicable for Japanese patients but the subgroup classification on intermediate risk could be. Seo and colleagues¹⁵ compared recurrence and progression rates between the EORTC risk tables and their own cohort of 251 Korean patients. All recurrence rates of the Korean patients were lower than in the

EORTC cohort, except for the 1-year recurrence rate in the intermediate-risk group, which was comparable with that of the EORTC cohort. In general, rates for progression in the Korean cohort were quite comparable with the rates in the EORTC risk tables despite the more aggressive patient and tumor characteristics of the Korean cohort. Hernandez and colleagues¹⁰ performed an external validation in 417 patients with primary NMIBC. In general, probabilities for both recurrence and progression in this cohort were higher than in the EORTC cohort. Their results validate the EORTC risk tables in terms of recurrence but not in terms of progression because of the low number of patients that progressed. Pillai and colleagues¹⁷ validated the EORTC risk model in 109 patients with primary and recurrent NMIBC. They found significantly higher 1- and 5-year probabilities of recurrence for all 4 groups compared with the EORTC model. However, it was not possible to draw firm conclusions about the validity because of the low number of patients in the individual groups.

In all, it is likely that the recurrence and especially progression rates reported by the EORTC risk tables are higher than those found in current clinical practice. As mentioned earlier, the progression probabilities and to a lesser extent the recurrence probabilities mentioned in the EORTC study are likely to be similar to the untreated natural history of the disease.

OTHER BC PROGNOSTIC MODELS

There are many prognostic models for NMIBC^{19–26} as well as for muscle-invasive disease.^{27–33} In this section, the authors discuss some of the other prognostic models for NMIBC. The prognostic models on MIBC are not discussed.

Club Urológico Español de Tratamiento Oncológico Scoring Model

The scoring model from the Spanish Urological Club for Oncological Treatment (Club Urológico Español de Tratamiento Oncológico [CUETO]) is the most commonly known prognostic model for NMIBC besides the EORTC risk tables. Fernandez-Gomez and colleagues²⁶ used the data of 1062 patients treated with BCG in 4 studies between 1990 and 1999. All patients received BCG maintenance treatment regimens (12 instillations within 5–6 months after TURBT) and had identical follow-up schedules, but the BCG dose did differ (13.5–81.0 mg). Only 4.2% received less than 6 BCG instillations, and less than 30% of patients discontinued therapy. The median follow-up was 69 months. In total, 346 patients

(32.6%) had recurrences, and 142 patients (13.4%) had progression to muscle-invasive disease. Prognostic factors for time to recurrence were gender, age, tumor status, number of tumors, associated CIS, and grade. For time to progression, age, tumor status, T category, and grade were of significant influence. A scoring system from 0 to 16 was developed for recurrence and from 0 to 14 for progression. Then recurrence and progression probabilities at 1, 2, and 5 years were calculated. Finally, these probabilities were compared with the EORTC recurrence probabilities. All recurrence probabilities were lower in the CUETO model than in the EORTC model. The progression probabilities were lower for high-risk patients; but in most intermediate-risk patients, the 2 scoring systems gave similar progression probabilities. As mentioned in the discussion by Fernandez-Gomez and colleagues,¹³ limitations of this study are the retrospective analyses and the use of the old TNM classification. Furthermore, no re-TURBT or immediate postoperative instillations were done, and the parameters of possible influence that were missing in the EORTC risk tables, such as tumor location, are also missing in the CUETO scoring model. Also, an internal validation to test accuracy is lacking and, as mentioned in the editorial comment, the lower significance of CIS is likely to be caused by the small number of patients with CIS. The sensitivity of this scoring model is 60%, the NPV is 92%, but the PPV is only 24%.

Rosevaer and colleagues³⁴ conducted an external validation of the CUETO model in 718 patients treated with BCG plus interferon-alpha. The 3-year RFS was much lower in this study than in the CUETO study. However, comparing RFS between the 4 groups categorized according to the CUETO score showed a significant difference between the groups ($P < .001$). Therefore, the discrimination when using this scoring model is good. Nevertheless, currently accepted practices, such as immediate postoperative instillations, re-TURBT, and long-term maintenance BCG instillations, were not taken into account for both this group and the CUETO model, which is of influence on the clinical outcome of these patients.

Other Prognostic Models for NMIBC

Besides the most well-known EORTC risk tables and the CUETO scoring model, several other models have been developed^{19–24}, but because these models are not commonly used in daily practice, they are beyond the scope of this review. However, in general, the most frequently cited

prognostic factors for the time to first recurrence are the number of tumors, whether the tumor is primary or recurrent, and if recurrent, the prior recurrence rate and the tumor size. For the time to progression to MIBC, the most important prognostic factors are grade, stage, and the presence of CIS. The most frequently cited prognostic factors for the course of the disease in patients with CIS are age, response to BCG, type of CIS (primary, secondary, concurrent), extent of CIS (unifocal, multifocal, or diffuse), the presence of irritative bladder symptoms, hematuria, and extravesical extension.³⁵

USE OF PROGNOSTIC MODELS IN UROLOGICAL PRACTICES

In general, a good prognostic model discriminates between disease and illness, gives an accurate prognosis, has a good calibration, is generalizable, and is easy to use. Good sensitivity and specificity are required for proper discrimination. But, depending on how the model will be used, the NPV and PPV might be more important than sensitivity and specificity. The accuracy of a model can be assessed by internal validation (apparent validation, split-sample validation, cross-validation, or bootstrapping) or, even better, by external validation with a new cohort. The latter also tests the generalizability of the model. A model with a good calibration has a good agreement between the observed/true outcome and the predicted outcome.³⁶ Unfortunately, none of the existing prognostic models for NMIBC have all of these requirements. Common problems are overfitting of the model because validation is done on the data used to derive it from, leading to a poor generalizability, a low c index, or a poor calibration when applied to external datasets, resulting in either overtreatment or undertreatment of patients, which is not in concordance with the current treatment guidelines. And if the c index or calibration is high, the next question is whether it is high enough to justify the use of the model in clinical practice.

For use in daily practice, other variables, such as patient comorbidity and risk of major surgery, are also important in making a final decision on which treatment best suits a given patient. Another current problem is the lack of validation. Prognostic models that have not had an external validation are less reliable and clinicians may be less eager to incorporate them into their clinic workflow. Practice patterns are also very difficult to change. The very practical nature of a busy clinic may undermine the provider's use of any prognostic models unless it is readily incorporated

into an electronic health record that will automate the calculation of risk category or disease outcome. It is likely that urologic trainees exposed to these models during their residency and fellowship will use them, or subsequent versions, later in practice. All these factors are responsible for the fact that few urologists currently use prognostic models in their daily practice.

Some risk models, such as the EORTC risk tables, are incorporated into guidelines. But guidelines are not commonly followed, as shown by Chamie and colleagues.³⁷ They investigated practice patterns concerning treatment in 4545 American patients with high-grade NMIBC. The American guideline, the European guideline, and the National Comprehensive Cancer Network's (NCCN) guideline were all investigated for their use in daily practice. An extremely low number of patients received all the diagnostic and therapeutic steps in concordance with the guidelines, namely, only one patient. However, 25.8% of patients did receive 6 or more instillations with BCG. Upper tract imaging and a single postoperative instillation with intravesical chemotherapy were especially lacking.

Despite the disadvantages of the prognostic models, clinical reasoning is not flawless; omission bias (bias against action) and outcome bias (it is easier to evaluate outcome than it is to evaluate a decision process) can influence treatment decisions,³⁸ and medical doctors tend to recommend the treatment they deliver themselves.³⁹ Several studies have shown that predicting clinical outcome by medical doctors is less accurate than when using prognostic models.^{40,41}

The International Bladder Cancer Group (IBCG) recognized these flaws and provided uniform terminology and recommendations for the risk classification and management of patients with NMIBC.⁴² Based on the 4 existing guideline recommendations (EAU, AUA, NCCN, and First International Consultation on Bladder Tumors guidelines), they developed a simple algorithm for the treatment and management of patients with primary NMIBC based on 3 easily definable risk groups: low risk was defined as a solitary, primary low-grade pTa tumor, whereas high risk was any pT1 and/or high-grade tumor and/or CIS. This model is a fine example of a useful model for day-to-day urological practice. However, the algorithm is only for primary patients, and recommendations for the management of treatment failure and recurrence are less clearly defined because of the major differences between the 4 guidelines.

Should we then decide to stop developing and using prognostic models? The authors of this

article do not advise to stop, but statistical concepts, such as discrimination (c index, AUC), calibration, *P* values, hazard ratios, odds ratios, and even sensitivity and specificity, do not really help clinicians when it comes to making clinical decisions in a given patient. It remains very important to give an adequate treatment as soon as possible because delay and inadequate therapy are associated with a worse outcome.^{43–45} The authors discuss their view on improving the use of prognostic models in the next paragraph.

FUTURE PERSPECTIVES ON BC PROGNOSTIC MODELS

Before developing new models, one should carefully think about the clinical purpose of the model: what is the goal of the prognostic model and how will it be used in clinical practice? For BC, one could consider to try to identify high-risk patients for immediate cystectomy or to identify low-risk patients who do not need further treatment or would be candidates for low-intensity surveillance. When developing a model, clinically meaningful statistics should be used, such as PPV and NPV. For example, the PPV of the EORTC risk tables for progression in high-risk patients is only 21%, which means that if a patient is classified as high-risk and would go for cystectomy, this would be overtreatment in 79% of the cases. Thus, the EORTC risk tables are not useful for determining what the best treatment is for high-risk patients.

One option is to update the existing models with data that were not previously available. Data on recent advances that are currently recommended by the guidelines should be included in the current models, such as data on re-TURBT, fluorescence cystoscopy, and postoperative instillations. External validation should always be performed when a prognostic model is to assess its generalizability.

As mentioned by Shariat and colleagues,⁴⁶ larger data sets, better data collection methods, and more sophisticated modeling procedures are needed to improve predictive accuracy. In addition, better accuracy might be accomplished by modeling physician- or hospital-specific data for patients being treated by that physician or at that hospital. Finally, prognostic models that predict the likelihood of metastatic progression, cancer-specific mortality, and the long-term quality of life are likely to have great utility for patients and physicians when exploring treatment alternatives.

Should we update models by combining patient and tumor characteristics with biomarkers? Ideally, biomarkers should help to identify patients at high risk of recurrence and could, therefore, increase

the accuracy of prognostic models. Several groups have already attempted to combine biomarkers to improve the outcome of NMIBC.^{16,21,47–49} Shariat and colleagues²¹ combined their nomogram with nuclear matrix protein 22 (NMP22). This combination had a good accuracy (AUC >80%), but the investigators did not compare models with and without NMP22, so the additional value of adding NMP22 was not investigated. Another example of combining a biomarker with clinical data is the previously mentioned article of Van Rhijn and colleagues¹⁶ in which they combined molecular grading (FGFR3 gene mutation status and MIB-1 expression) with the EORTC risk scores. They found an additional value of this combination: the predictive accuracy of the EORTC risk scores increased from 74.9% to 81.7%. Members of this group also combined 4 molecular markers (FGFR3 gene mutation status, Ki67, P53, and P27 expression) with T1 substaging (2 types: T1e vs T1m and T1a vs T1b vs T1c) and EORTC risk scores.⁴⁹ P53 was not of any value, and the additional value of the other 3 markers was only 1.3% (*P* > .05). However, the T1e/T1m substaging was one of the most important variables for progression.

Before adding biomarkers to prognostic models, we should take into account which (statistical) steps are necessary to make a model of additional value. According to Sylvester, 4 steps are needed: first the identification of interesting biomarkers, then the defining of a function used to combine the biomarkers together into a classification rule, next a validation to show its reproducibility, and finally investigating whether the biomarkers improves the predictive accuracy of the model.⁵⁰ Also, we should investigate whether we need one biomarker or a panel of markers. We have to improve the scientific rigor related to biomarker evaluation and testing and the feasibility of their use in day-to-day clinical practice as compared with the currently available biomarkers.

Another, and perhaps the best, possibility would be to simplify the current prognostic models to make them more useable in daily practice. We should improve their PPV and/or NPV and pay more attention to calibration, as suggested by Sylvester.⁵⁰ Classification tables including NPV and PPV express the results of prognostic models in clinical terms and can be used to compare them. Once there is a model that is clinically useful (ie, with high NPV and PPV) the model should be evaluated. As mentioned earlier, *P* values, hazard ratios, c index, and so forth have little or no direct consequences for day-to-day practice. A more relevant method has been suggested by Vickers and Cronin⁵¹ to calculate the net benefit of a new model compared with the standard model as

part of a decision curve analysis. This analysis is based on 2 principles: models may influence medical decisions and decisions have consequences that can be directly incorporated into analyses by using weights. Decision analytic techniques may be used to determine whether a model is worth using at all, which of the 2 (or more) models is preferable, and whether an additional predictor is worth measuring.

If we know what the important prognostic factors in a certain group of patients are, we can personalize their treatment based on their level of risk. As mentioned earlier, the IBCG has already published a simple algorithm for the treatment and management of patients with primary NMIBC.⁴² The EAU NMIBC Guidelines Panel is working to simplify the risk group definitions for their day-to-day use in the clinic. The EORTC will be updating their risk tables in patients treated with maintenance BCG, and several authors of this article are working on outcome probabilities after intravesical chemotherapy. All of these are practical examples of work that is being done to make it easier for clinicians to classify patients according to their level of risk and, thus, to provide the most appropriate treatment in individual patients.

SUMMARY

Currently, there are many prognostic models available for NMIBC but they are not commonly used in daily practice because of their complexity and limited usefulness in treatment decision making. To make prognostic models more useful, the focus should be on the clinical implications of the model for the patient, such as by focusing on NPV and PPV rather than *P* values, sensitivity, and specificity. The net benefit of a model should be compared with the standard model by means of classification tables and decision analytic techniques to test its additional clinical value. Currently, biomarkers do not have sufficient additional value, and markers under investigation should first stand the test of time.

Ultimately, even good models will not be translated into clinical practice unless they can be integrated into the standard clinical workflow and prove their importance in improved therapeutic results. Despite the efforts of many, these predictive models have not replaced a practicing clinician's treatment experience.

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Urinary Markers/Cytology

What and When Should a Urologist Use

Jeffrey M. Tomasini, MD, Badrinath R. Konety, MD, MBA*

KEYWORDS

• Non-muscle invasive bladder cancer • Cytology • UroVysion FISH • NMP22 • BTA • ImmunoCyt

KEY POINTS

- 80% of urothelial carcinoma is non-muscle invasive at diagnosis, and up to 70% will have recurrence within 5 years.
- Urine-based tumor markers are an important adjunct in both screening and surveillance of urothelial carcinoma.
- Cystoscopy remains the most cost-effective method for identifying bladder cancer recurrence.
- Urine cytology is highly specific but lacks sensitivity in detection of non-muscle invasive bladder cancer.
- Use of urine tumor markers may best be served when cytology is indeterminate or likely to be inaccurate.

INTRODUCTION

It is estimated that there are 585,390 people in the United States living with bladder cancer, and an additional 73,510 cases will be newly diagnosed in 2012. As of 2012, bladder cancer is the fourth most common cancer afflicting men and ninth most common cancer in women.¹ Nearly 80% of all bladder cancer diagnoses are non-muscle invasive at presentation.² Of patients with non-muscle invasive urothelial carcinoma, 50% to 70% will have at least one recurrence in 5 years, and up to 20% will progress to a more advanced stage during that time.³ Identifying a test to both screen and facilitate surveillance for bladder cancer is of paramount importance. At present, diagnosis and surveillance of urothelial cancer includes imaging of the upper urinary tracts with computed tomography (CT) urography, urinary cytologic evaluation, and cystoscopy.

A test that is inexpensive, noninvasive, and reproducible and that provides excellent sensitivity and specificity is an ideal candidate for a screening marker. Currently, there are 4 Food and Drug Administration (FDA)-approved bladder cancer tumor markers available for use in the United States. These have been used with varying success.

However, the data regarding the consistency and reliability of these markers have been mixed, and the precise role for these new markers other than cytology is yet to be clearly defined. Some of these markers are also more expensive than urine cytology and even cystoscopy. Thus, it is imperative to clearly define a strategy for using these tests in the diagnosis and follow-up of both non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer.

CYTOLOGY

Urinary cytology, first described for use in evaluating urothelial cancer in 1945 by Papanicolaou,⁴ has been a standard test in the evaluation of bladder cancer. A urine sample is collected, centrifuged, and the sediment resuspended, stained, and evaluated with light microscopy (**Fig. 1**). The sample is then read by a pathologist who classifies the sample as normal, atypical, or indeterminate; suspicious; or malignant.⁵ A malignant sample was previously assigned a grade of 1, 2, or 3. The new standard is to designate a malignant sample as either low-grade or high-grade based on architectural and cytologic criteria to reduce ambiguity and improve interobserver reproducibility.⁶

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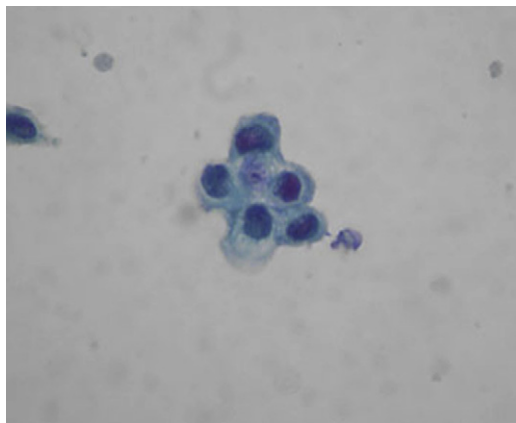


Fig. 1. A voided urine sample revealing low-grade urothelial carcinoma.

Several factors affect the utility of urinary cytology. Cancer cells must be sloughed into the urine to be collected. High-grade cancers are more apt to slough into urine than low-grade cancers because of weaker intercellular attachments.² The sample is subjectively diagnosed and graded by a cytopathologist, and as such there is both interobserver and intraobserver variability. Inflammatory conditions of the bladder including cystitis and bladder calculi can affect the results.⁷ Given these factors, sensitivity of urinary cytology for non-muscle invasive disease is quite variable. Pooled data reveal overall sensitivity for non-muscle invasive disease ranging from 29% to 77%. Overall specificity of cytology ranges from 71% to 100%, with most studies reporting more than 90% specificity for both low-grade and high-grade urothelial cancer.^{8–13}

One of the problems with interpreting urine cytology is that the result is sometimes ambiguous. A result of atypical, atypical suspicious, or suspicious is hard to judge and use in

management decisions.¹⁴ Individuals who have undergone recent instrumentation or have evidence of inflammation or stone disease may demonstrate an atypical cytology. However, if these individuals also have a history of urothelial carcinoma, the interpretation of the urine cytology reading is difficult. This could lead to unnecessary work up and related morbidity and cost. The use of some of the alternative urine-based markers could potentially serve to improve the accuracy of urine cytology or arbitrate indeterminate results.

UROVYSION (FLUORESCENCE IN-SITU HYBRIDIZATION)

The UroVysion (Abbott Molecular Inc, Des Plaines, IL, USA) test uses fluorescence in-situ hybridization (FISH) to detect increased copy numbers, or aneuploidy, of chromosomes 3, 7, and 17, as well as homozygous deletions of loci at chromosome 9p21.¹⁵ A positive test is determined by presence of either (1) 5 or more cells with 2 or more chromosomal gains (chromosomes 3, 7, 17), or (2) 12 or more cells with gain of a single chromosome, or (3) 12 or more cells with homozygous detection of 9p21 locus (**Fig. 2**).^{16,17} False-positive results can occur when a barbotage sample is used because of probe uptake in multinucleated umbrella cells, which are dislodged and can be falsely elevated in barbotage specimens. These cells typically constitute only 2% of the cells in a urine sample,¹⁸ but up to 11% in a barbotage sample.¹⁹ Other explanations for a false-positive FISH include the presence of an inclusion body such as a polyoma virus and seminal vesicle cells. False-negative FISH is seen in the presence of degenerated cells, hyphae, excess lubricant, squamous cells, and autofluorescent bacteria. Positivity with aneuploidy of chromosomes 7 and 17 is more commonly associated with the presence of tumor compared with

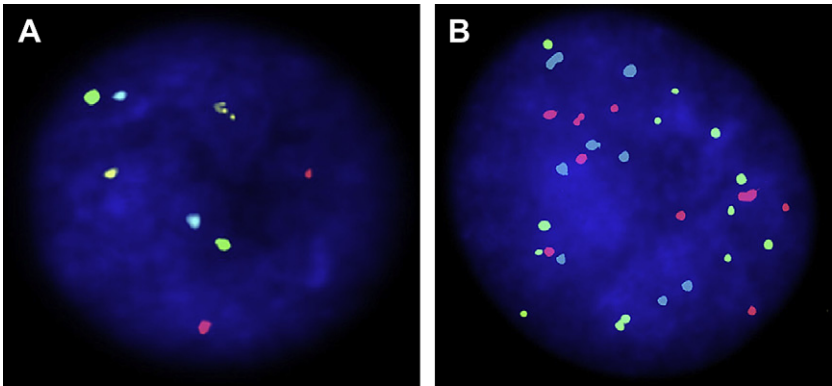


Fig. 2. UroVysion FISH test of voided urine. (A) A negative test with 2 copies of each probe present. (B) A positive test with multiple copies of each probe visible.

positivity with aneuploidy of chromosome 3 or loss of 9p21. The loss of 9p21 is also more commonly associated with the presence of low-grade, non-muscle invasive tumors. Additionally, the result of an UroVysion FISH test may be positive in the absence of a positive cystoscopic or cytologic evaluation; this occurs in 35% to 63% of patients up to 6 to 20 months before development of a macroscopically visible urothelial malignancy and has been deemed an “anticipatory positive” FISH test.^{13,20–22}

UroVysion FISH is more sensitive for high-grade and invasive urothelial malignancies, with reported sensitivity ranging between 83% and 100%. It is also fairly sensitive at detecting non-muscle invasive tumors, with sensitivity ranging from 64% to 76%. UroVysion FISH is nearly as specific as urinary cytology with reported specificity ranging from 89% to 96%.^{8,13,23,24} FISH has also been shown to have utility in surveillance for urothelial carcinoma recurrence after intravesical bacillus Calmette-Guerin (BCG) therapy. Both cystoscopy and cytology are often inconclusive following BCG therapy because of the confounding effect of BCG-induced inflammation. Patients with a positive FISH following BCG therapy have demonstrated nearly 10-fold higher likelihood of muscle invasive disease as compared with patients with a negative FISH after BCG.²² A positive FISH test after intravesical BCG therapy is also associated with a higher likelihood of nonresponse to BCG and recurrent tumor (**Table 1**).

More recently, UroVysion FISH has also been used to adjudicate the results of urine cytology, which are read as “atypical.” Given that FISH examines the chromosomal abnormalities in a cell that are less susceptible to conditions that may affect cell morphology such as inflammation or BCG therapy, it may serve as an attractive second level test in patients with hard to interpret urine cytology results. Schlomer and colleagues²⁵ examined the utility of reflex FISH testing in 120 patients with atypical urine cytology. They

found that in patients with a positive cystoscopy, additional FISH testing was of little value. In those with an equivocal cystoscopy or with a negative cystoscopy, the negative predictive value (NPV) of FISH was 100%. They concluded that reflex FISH testing could eliminate the need for further workup and biopsy in patients with an atypical cytology, negative FISH and equivocal or negative cystoscopy. They found no patients with an atypical cytology and a false-positive FISH test.

FISH testing has also been able to detect patients with bladder cancer of nonurothelial histology as well as cancers in adjacent organs such as colon and prostate.²⁶ Sensitivity for detection of adenocarcinoma is as high as 79%. FISH testing of other body fluids such as pleural effusion fluid can help detect tumor cells.²⁷

NUCLEAR MATRIX PROTEIN 22

Nuclear matrix proteins (NMPs) are structural components of the cell nucleus, and also function in regulation of gene expression and DNA replication. NMP22 is a protein specific to mitosis and is involved in the distribution of chromatids to daughter cells. The concentration of NMP22 has been shown to be up to 25 times greater in bladder cancer cell lines than normal urothelium.²⁸ Inflammatory conditions including cystitis, pyuria, urolithiasis, and hematuria can result in elevated urinary NMP22 levels.²⁹ NMP22 is available as a point-of-care assay called BladderChek (Stellar Pharmaceuticals, Inc, London, Ontario) (**Fig. 3**) that provides immediate results at half the cost of urine cytology.³⁰

Several studies have evaluated patients with NMP22 and have examined cohorts that were further subdivided as superficial and invasive disease. Sensitivity of NMP22 in non-muscle invasive disease ranged from 54% to 63% and 70% to 100% sensitive for muscle invasive disease. Overall specificity of NMP22 in urothelial carcinoma ranged from 55% to 90%.^{8,11,31–33} Grossman,

Table 1 Utility of urinary FISH testing in assessing response to intravesical BCG therapy					
	No. Patients	Tumor Recurrence Post-BCG (%)	Tumor Recurrence Post-BCG		
			Positive FISH with Recurrent Tumors	Negative FISH with Recurrent Tumors	% MIBC (≥T2)
Kipp et al, ²² 2005	37	67	100%	52%	58
Whitson et al, ⁵⁸ 2009	42	43	89%	26%	5
Mengual et al, ⁵⁹ 2007	65	36	52%	25%	10
Savic et al, ⁶⁰ 2009	68	38	76%	26%	
Kamat et al, ⁶¹ 2012	126	31	50%	18%	28



Fig. 3. The BladderChek NMP22 point of care test.

and colleagues³⁰ evaluated 1331 patients at high risk for urothelial carcinoma with NMP22, cytology, and cystoscopy. Seventy-nine cancers were biopsy proven, 62 of which were non-muscle invasive disease. The sensitivity of NMP22 in this group was 50% compared with 16% for cytology.

A Canadian group prospectively evaluated patients with high-risk superficial disease (tumors that are high-grade, carcinoma in-situ or T1, >3 cm, and recurrent disease at initial 3-month cystoscopy) with NMP22. Fifteen patients out of 94 tested had a positive NMP22 test result and 9 of the 15 patients developed a subsequent recurrence (60%), which is compared with 30 patients with recurrence and a negative NMP22 test (37%). The group concluded that NMP22 may be helpful to risk-stratify patients on surveillance, but NMP22 results in this population did not predict progression-free survival or overall survival.³⁴ The combination of cystoscopy and NMP22 has been shown to have a higher sensitivity than the combination of cytology and cystoscopy (99% vs 94%), which along with the immediate availability of results, makes it more attractive to use NMP22 BladderChek as an adjunct to cystoscopy.³⁵ However, the higher false-positive rate of NMP22 has hampered the wide adoption of this approach.

NMP22 along with other markers has also been used in several studies testing the concept of screening for bladder cancer. The ease of use and rapid availability of the results from the NMP22 BladderChek test render it attractive in this context. However, results from the studies

suggest that the BladderChek test does not significantly aid in identification of patients with bladder cancer.^{36,37} The false negative rate of NMP22 was found to be too high. NMP22 can also yield false-positive tests in the presence of inflammation and hematuria, which raises concerns regarding its use in the setting of screening.

BLADDER TUMOR ANTIGEN

The bladder tumor antigen (BTA) test is available in 2 formats: BTA stat and BTA TRAK (Polymedco, Inc, Cortlandt Manor, NY, USA). Both assays detect complement factor H-related protein in urine, which is responsible for preventing activation of the complement cascade. This test is based on a presumed selectivity of bladder cancer cells to avoid immunologic detection, and complement factor-H related protein is not found in normal bladder cancer cells.^{38,39} BTA stat is FDA approved for surveillance, but not initial diagnosis of bladder cancer, and is provided as a point-of-care qualitative assay similar to that of NMP22 (Fig. 4). Results are provided in less than 30 minutes. BTA TRAK is a quantitative standard enzyme-linked immunosorbent assay.² False-positive results may occur in presence of hematuria, urolithiasis, inflammation, and recent urologic instrumentation.^{17,40} Intravesical BCG therapy has also been associated with false-positive BTA tests.^{41,42}

In a meta-analysis that included numerous studies evaluating BTA stat, the sensitivity of this rapid point-of-care test for non-muscle invasive urothelial carcinoma ranged from 45% to 75%.⁸ The BTA stat test was significantly more sensitive for muscle invasive disease, sensitivity ranging from 67% to 100%. Overall specificity of this test was 64% to 89%.^{8,9,11,23,24,31,33,43-45}

IMMUNOCYT

ImmunoCyt/uCyt+ (Scimedex, Corp., Denville, NJ, USA) is an assay using fluorescent-labeled antibodies to 3 glycoprotein antigens commonly



Fig. 4. The BTA stat point of care test.

found on urothelial carcinoma cells. Texas red stain (red) is used to identify 19A211, a high molecular weight form of carcinoembryonic antigen (Fig. 5). Fluorescein-tagged antibodies (green) are directed at mucins LDQ10 and M344, both of which are specific to cancer cells.⁴⁶ A test is considered positive if at least one cell has a green or red fluorescence and negative if no fluorescently labeled cells are identified after counting 500 cells.⁴⁷ Limitations of ImmunoCyt include necessity to evaluate at least 500 cells per slide to ensure a complete evaluation, difficult detection of green fluorescence when present in low concentration, and requirement of adequate training to perform and read the test.⁴¹

The antigens detected by ImmunoCyt are commonly present even on low-grade and non-muscle invasive tumor cells. M344 is expressed in 71% of Ta and T1 tumor cells, and 19A211 is detectable in 90% of the same tumor cells.⁴⁸ Sensitivity of ImmunoCyt in non-muscle invasive urothelial cancers is 60% and increased to 80% for muscle invasive cancers. Overall specificity is 78%.¹⁰ Sensitivity for low-grade tumors increased to 79% when ImmunoCyt is performed in addition to urinary cytology and to 99% for high-grade tumors.⁴⁹

ImmunoCyt has been combined with urine cytology to enhance the sensitivity and specificity of urine cytology. The combination of the 2 tests has been used particularly effectively in reducing the frequency of surveillance cystoscopy in patients with low-grade non-muscle invasive disease.^{49,50} ImmunoCyt has also been used as a second level test to arbitrate atypical cytology.⁵¹ A reflex ImmunoCyt test appears to be able to

predict the findings on cystoscopy in patients with atypical cytology. A reflex ImmunoCyt test had an NPV of 90% in those with a prior history of urothelial carcinoma, whereas in those without such a history, reflex ImmunoCyt had an NPV of 94%.

DISCUSSION

Bladder cancer has a very high recurrence rate, up to 70% within 5 years of initial diagnosis.³ As such, patients with bladder cancer require close surveillance for a prolonged period of time. Cystoscopy is the gold-standard modality for detection of recurrence of bladder cancer. Although it is generally well tolerated, cystoscopy is an invasive procedure. The high rate of tumor recurrence in bladder cancer mandates a frequent surveillance interval, thus many patients undergo cystoscopy several times per year. This has resulted in bladder cancer being the most expensive malignancy to treat per patient from diagnosis to death.⁵²

Most bladder cancers are detected on evaluation for gross hematuria. Three quarters of these tumors are non-muscle invasive at diagnosis. Institution of a screening program, particularly in high-risk populations such as heavy smokers or those with occupational exposure, would ideally identify tumors earlier than if presenting with gross hematuria, thus decreasing the rate of invasive disease at diagnosis. Using mathematical modeling, Lotan and colleagues⁵³ determined that screening is cost-effective for bladder cancer. Several studies have prospectively evaluated the efficacy of screening for bladder cancer. Steiner and colleagues³⁶ screened 183 patients deemed high-risk based on smoking history greater than 40 pack-years. Urine dipstick for microscopic hematuria, cytology, NMP22, and UroVysion were used for screening, and a positive result in any test led to cystoscopy and CT urography for diagnosis. This resulted in diagnosis of 6 malignancies, half of which were of the upper tracts. One false-negative result was identified. Use of urine dipstick, cytology, and UroVysion was recommended for screening in high-risk patients.

Cancer screening programs should be cost-effective, and the prevalence of disease must be sufficient within a population to justify testing. Lotan found a significant improvement in overall survival, downstaging of disease, and cost reduction when incidence of bladder cancer was more than 1.6%.⁵³ However, these studies that have used marker-based screening have not proved very effective. One reason has been the relatively low prevalence of the disease in a general population. More effectively, identification of an “at risk”

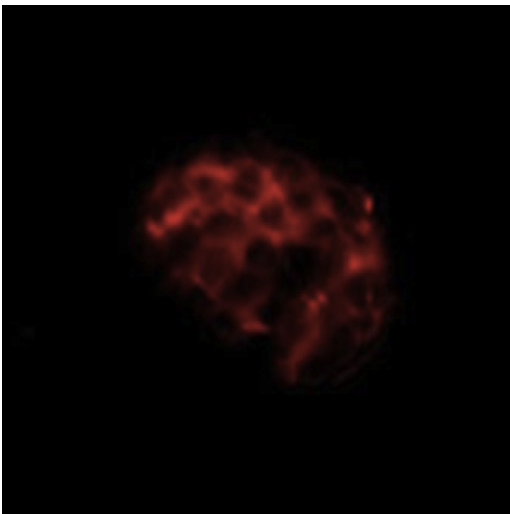


Fig. 5. Positive ImmunoCyt test of a voided urine specimen.

population and availability of better makers with higher specificity while retaining the ease of use of the currently available point of care tests such as NMP22 BladderChek may ultimately help facilitate these efforts.

BTA stat and BTA TRAK, NMP22 and NMP22 BladderChek, UroVysion, and ImmunoCyt tests are currently the only FDA-approved urine-based bladder tumor markers. These tests are all approved for use in surveillance of bladder cancer, and with the exception of ImmunoCyt, for the initial diagnosis of bladder cancer as well. To be effective in replacing cystoscopy for the surveillance of NMIBC, a urinary tumor marker should have high sensitivity and a low false-negative rate or a high NPV. The sensitivity (63%–76%) and NPV for markers such as FISH are high (>80%). However, this level may not be sufficient for most patients. Surveys of patients undergoing cystoscopic surveillance indicate that 75% of patients would require a test to have a sensitivity greater than 95%, and an additional 21% would accept a marker sensitivity of 90% to 95% before foregoing cystoscopic surveillance.⁵⁴ None of the currently available markers are able to achieve this level of sensitivity consistently. Hence at this time, eliminating cystoscopy from surveillance of NMIBC does not appear to be a viable option. Cystoscopic surveillance may also be the most cost-effective method of monitoring NMIBC at this time. In a prospective trial of 200 patients with prior diagnosis of non-muscle invasive bladder cancer, patients underwent surveillance cystoscopy as well as evaluation with urinary cytology, NMP22 BladderChek, and UroVysion FISH.⁵⁵ The investigators concluded that cystoscopy remains the most cost-effective method to identify bladder cancer recurrence. Detection was not improved with addition of these markers to cystoscopy and simply added to cost. The cost per tumor detected by cystoscopy alone was \$7,692, compared with \$11,143 for cystoscopy and NMP22, \$19,111 for cystoscopy and UroVysion, and 10,267 for cystoscopy and cytology.⁵⁵ Hence the International Consultation on Urologic Diseases – European Association of Urology panel concluded that at this time white light cystoscopy remains the most cost-effective method of surveillance of the lower urinary tract for tumor recurrence.⁵⁶

Future applications of urinary markers can be designed based on the type of marker, that is, protein-based or cytologic/molecular. Protein-based markers tend to lend themselves to point of care determination, which is most attractive for use in the context of screening and perhaps even patient self-testing. These tests are also

more easily applied during episodes of surveillance as the results are more immediately available and clearly defined without a gradation between positive and negative as can be the case with urine cytology. At least one study suggests that availability of the results of urinary marker testing at the time of surveillance can lead to higher rates of biopsy/resection and recurrence detection.⁵⁷ This represents a diagnostic review bias that favors use of urinary markers at the time of cystoscopy. Cytologic or molecular markers on the other hand, may have more prognostic ability. They could optimally be applied for assessment of tumor response to intravesical therapy and to determine risk of progression. They could also be better used to arbitrate atypical or suspicious urine cytology readings. Reflex testing of all specimens with an atypical reading could lead to reduced diagnostic workup and therefore reduced morbidity and costs.

Over the past 2 decades, significant efforts have been made to identify and apply urinary tumor markers to enhance the diagnosis of bladder cancer and to overcome the shortcomings of urine cytology. Although several attractive markers have been identified, follow-up studies and phase IV post-FDA approval clinical experience have not consistently borne out the initial favorable results; this has led to confusion regarding optimal applicability of these markers. With continued careful study, it is very likely that we will define more precise indications for the use of these markers. At the current time, they seem most appropriate for use as an adjunct to cystoscopy, particularly in situations where cytology is likely to be inaccurate (eg, postintravesical therapy, inflammation) or if cytology is itself indeterminate. They could also be used if cytology is hard to obtain or unreliable.

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Office-based Bladder Tumor Fulguration and Surveillance Indications and Techniques

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KEYWORDS

• Bladder cancer • Fulguration • Electrocoagulation • Laser • Recurrence

KEY POINTS

- Low-grade (LG) noninvasive bladder cancer is a heterogeneous disease with variable recurrence and progression rates, and helpful tools are available to appropriately risk-stratify patients.
- Substantial cost is accrued from management of recurrent LG bladder cancer in operating rooms.
- Office-based management of LG noninvasive bladder cancer is a cost-effective, well-tolerated, and safe strategy when applied to suitable patients.

INTRODUCTION

Bladder cancer is the fourth most common malignancy among men in the United States, with 52,050 expected newly diagnosed cases in 2011 and 17,320 cases among women. Although 14,990 deaths were expected during the same time period, most cases of bladder cancers are noninvasive and LG.^{1,2} Despite the low risk for lethality, non-muscle invasive bladder cancer (NMIBC) has a substantial risk for recurrence and progression occurs in some cases.³

Recurrent disease has long been managed with resection and fulguration.⁴ This is often performed in an operating room, resulting in significant expense, possible morbidity, and repeated exposure to general anesthesia. Some investigators have proposed alternative strategies for managing LG NMIBC, including office-based interventions in attempts to control cost and improve quality of life without exposing patients to unnecessary risks. This article examines the rationale, efficacy, and logistics of managing NMIBC in the office setting, thereby avoiding the need for intraoperative management for all recurrent LG NMIBC.

LOW-GRADE NON-MUSCLE INVASIVE BLADDER CANCER

In efforts to clarify confusion surrounding papillary bladder tumors, the World Health Organization and the International Society of Urological Pathology created a more stringent pathology classification scheme for bladder cancer. This system classifies non-muscle invasive papillary tumors into papilloma, papillary urothelial neoplasm of low malignant potential, LG, and high grade.⁵ There are significant differences in recurrence rates between tumors in this schema (**Fig. 1**).⁶ The risk for the first 3 of these groups for progression to invasive disease is low, with 0% to 1.2% for papillomas, 0% to 8% for papillary urothelial neoplasms of low malignant potential, and 5% to 13% for LG papillary tumors in contrast to progression rates greater than 45% for high-grade tumors.^{3,6–8} Although investigators report a variety of predictors for recurrence and progression, the strongest seem to include tumor stage, size, number, early previous recurrences, and presence of carcinoma in situ (CIS).³

The updated classification scheme provides additional information to better risk-stratify patients,

Disclosures: None.

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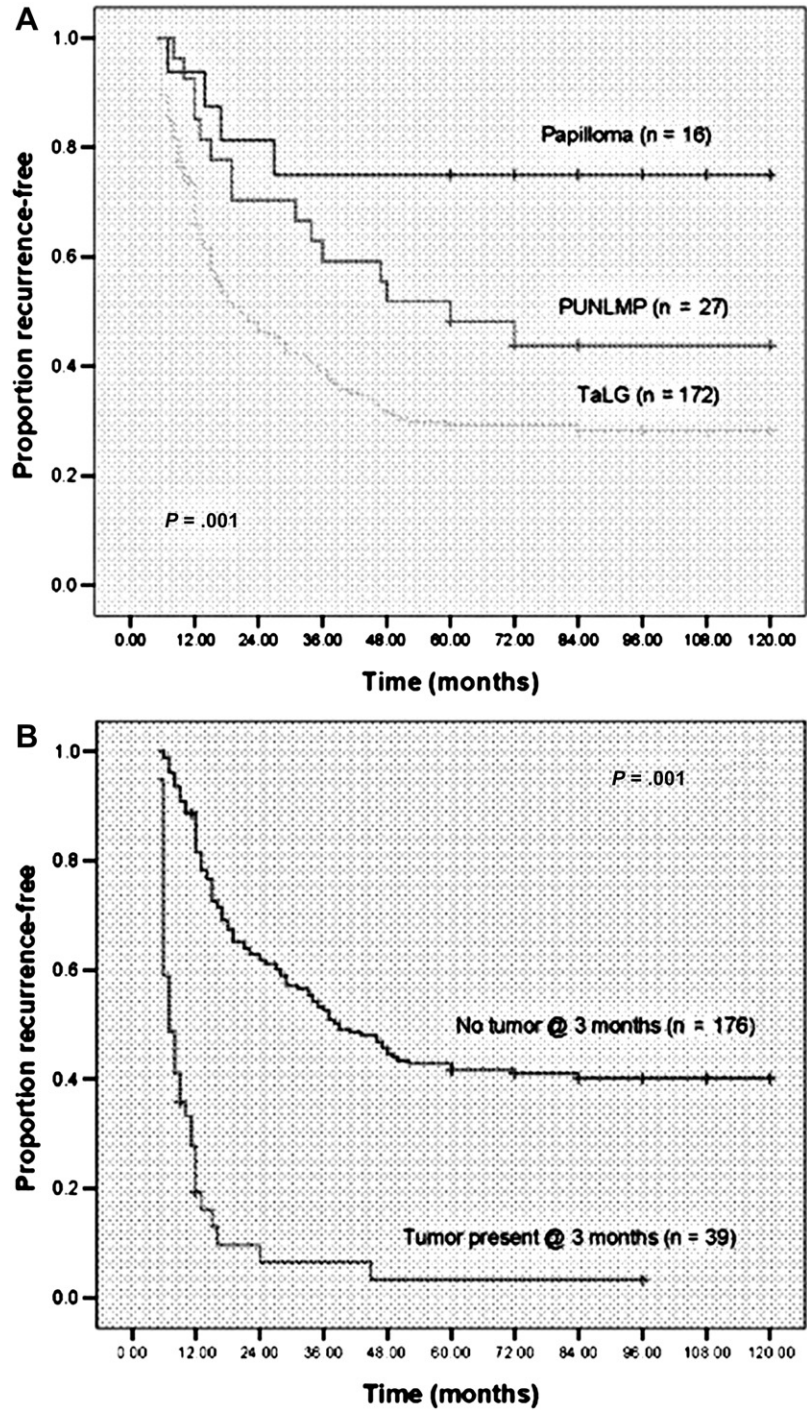


Fig. 1. (A) Recurrence-free survival by tumor type. (B) Recurrence-free survival by 3-month cystoscopy. (From Herr HW, Donat SM, Reuter VE. Management of low grade papillary bladder tumors. J Urol 2007;178(4 Pt 1):1201–5 [discussion: 1205]; with permission.)

distinguishing those who may need more-aggressive therapy from those who do not.⁹ Yet many perform cystoscopy every 3 months for the first 2 or 3 years, every 6 months for the following 2 years, and yearly thereafter, regardless of the risk of recurrence and progression. However, this strategy has not been shown more effective than less-rigorous surveillance protocols and subjects patients to frequent interventions that may not be of benefit and increase the cost of care. As a result, most argue for an approach tailored to patients' risk of recurrence and progression.¹⁰

Not all investigators agree with this approach. Leblanc and colleagues¹¹ presented data for patients initially diagnosed with Ta grade 1 disease and with follow-up of more than 5 years. They reported an overall recurrence rate of 55%, with 14% having recurrences more than 5 years from initial diagnosis. Progression to higher grade or stage was identified in 37%, but only 3.3% developed muscle invasive disease. These investigators argue for frequent cystoscopic evaluation continuing beyond 5 years.

VISUAL GRADING

An additional key to appropriately offer less-invasive treatment without harming those who require more-aggressive care is the ability to reliably differentiate between low-risk and high-risk tumors based on visual appearance. Herr and colleagues¹² found that experienced urologists were able to correctly identify 93% of lesions that had recurred after initial diagnosis of NMIBC as Ta grade 1 tumors. When voided urine cytology was added, accuracy increased to 99% for Ta grade 1 tumors. The investigators did not outline specific cystoscopic criteria that the performing urologist used but rather this determination was made by an overall impression of the surgeon based on experience. Other investigators have attempted to more rigorously outline criteria for higher-risk tumors. Satoh and colleagues¹³ found that tumors greater than 1 cm, those sessile in nature, and nonpapillary tumors were more likely to have muscle invasion.

COST

Management of bladder cancer has the highest cost of any malignancy per patient covered by Medicare, with lifetime costs per patient ranging from \$96,000 to \$187,000.¹⁴ When modeling for patients of all ages, including those younger than 65 years, another group estimated the lifetime costs for patients presenting with bladder cancer between \$99,270 and \$120,684. They found that

60% of these cost were related to surveillance and treatment of recurrences, with patients averaging 2.9 cystoscopies per patient per year.¹⁵

Study of cost-effective treatment of bladder cancer is limited and has not been incorporated into treatment guidelines.¹⁶ However, it is intuitive that substantial cost reductions may be achieved by shifting surveillance from frequent invasive procedures to less-frequent, risk-stratified protocols that use office-based management strategies in appropriately selected patients. Strategies that risk-stratify patients for surveillance cystoscopy and upper-tract imaging can reduce the frequency with which patients who have low-risk disease undergo costly and invasive procedures without exposing them to additional risk.¹⁷

Treatment and surveillance schedules for early-stage bladder cancer vary greatly by provider¹⁸ and higher intensity does not seem to prevent later treatments or need for major medical interventions, such as cystectomy. Furthermore, those who used high-intensity treatment and surveillance were more likely to use major medical interventions later on, contributing to higher costs.¹⁹

Office-based fulguration instead of resection in operating rooms has the benefit of avoiding outpatient facility, anesthesia, and pathologist fees in addition to decreasing patient time commitment and convalescence. Recognizing the potential cost savings of in-office procedures for the management of NMIBC, the Centers for Medicare and Medicaid Services increased physician reimbursement for office-based endoscopic procedures by a factor of almost 10 for office fulguration and by 3 for biopsy. However, in one faculty practice, this change in reimbursement did not decrease the overall cost for treating patients but instead resulted in an almost doubling in charges.²⁰

OFFICE-BASED MANAGEMENT

Several investigators have reported various approaches to office-based management of LG NMIBC with good outcomes. Outpatient fulguration with electrocautery of LG bladder tumors was described more than 30 years ago with substantial cost savings over inpatient management.²¹ Herr²² then described management of 185 patients with superficial bladder tumors using a flexible cystoscope, fulguration with a Bugbee electrode, and only local anesthesia. No patient requested that the procedure be stopped and at 24 months, 63% remained tumor-free. Wedderburn and coworkers²³ reported on office-based treatment of 103 consecutive patients with recurrent LG Ta lesions using only nonanesthetizing lubricant gel, with 80% reporting negligible or mild discomfort and only

2 patients reporting that they would have preferred the procedure to be done under a general anesthetic. No recurrence was found in 50.5%, with a median follow-up of 21 months, but 25.5% of those that recurred did so at the original treatment site. An update of the experience at Memorial Sloan-Kettering Cancer Center reported outcomes of office-based fulguration alone in 123 patients with recurrent NMIBC. Median follow-up was 6.84 years, and 73% had no evidence of disease, 21.7% were alive with disease, and 2.2% died from disease.²⁴

Variations on the use of traditional fulguration with electrocautery have been reported. Muraishi and colleagues²⁵ described using a biopsy forceps with electrocautery to simultaneously cauterize and obtain a specimen for pathologic evaluation. They subsequently updated this procedure by insufflating the bladder with CO₂, injecting the tumor with a mixture of 2% xylocaine and indigo carmine, and then resecting the tumor with hot biopsy cup forceps.²⁶

Use of the holmium:YAG laser alone or in combination with intravesical agents has also been reported for management of NMIBC. Jonler and colleagues²⁷ described ablation with a holmium laser in an office setting, using urethral lidocaine alone in 52 patients. No pain was reported in 86% and all stated they preferred this method to traditional transurethral resection (TUR). Unfortunately, no follow-up data were provided to assess the adequacy of treatment. Other investigators have reported limited follow-up but with acceptable recurrence rates.^{28,29}

In a nonrandomized study comparing holmium laser with traditional TUR, Zhu and colleagues³⁰ reported using the laser to resect rather than just ablate NMIBC under epidural anesthesia. They reported no difference in recurrence rate between the 2 therapies with mean follow-up of 34 months but with the advantage of fewer bladder perforations and bleeding complications. However, resection rather than ablation with laser may be too difficult or uncomfortable to do in the office and access to the laser generator in this setting may limit its use. For these and other logistical reasons, the authors favor office-based ablation with electrocautery rather than office-based holmium laser ablation.

PATIENT SELECTION

Proper risk stratification is critical for appropriate application of office-based management of NMIBC to those patients who are likely to benefit without exposing other patients to undue risk for recurrence or progression. Millan-Rodriguez and colleagues³¹ risk-stratified patients with NMIBC into low-risk,

intermediate-risk, and high-risk groups with good discriminative ability for recurrence, progression, and mortality using data from 1529 patients. The European Organisation for Research and Treatment of Cancer (EORTC) combined data from 7 randomized trials comparing treatments after initial diagnosis of Ta, T1, and CIS bladder cancer in more than 2500 patients to create tables that allow for calculation of short-term and long-term risks of recurrence and progression.³ Number of tumors, tumor size, prior recurrence rate, stage, presence of CIS, and grade are used to place each patient into a 4-tier risk group both for recurrence and progression at 1 year and 5 years (Tables 1 and 2). A calculator based on these data is available at: <http://www.eortc.be/tools/bladdercalculator/>.

Combining these tables with an experienced eye at determining recurrent LG bladder lesions based on appearance,¹² appropriate patients can

Table 1 Weights for calculating EORTC recurrence and progression scores		
Factor	Recurrence	Progression
Number of tumors		
Single	0	0
2 to 7	3	3
≥8	6	3
Tumor size		
<3 cm	0	0
≥3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 Rec/y	2	2
>1 Rec/y	4	2
T category		
Ta	0	0
T1	1	4
CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total score	0–17	0–23

Abbreviation: Rec, recurrence.
From Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49(3):466–5 [discussion: 475–7]; with permission.

Table 2
Probability of recurrence and progression according to total EORTC score

	Probability Recurrence, 1 y (95% CI)	Probability Recurrence, 5 y (95% CI)
Recurrence score		
0	15% (10%, 19%)	31% (24%, 37%)
1–4	24% (21%, 26%)	46% (42%, 49%)
5–9	38% (35%, 41%)	62% (58%, 65%)
10–17	61% (55%, 67%)	78% (73%, 84%)
Progression score		
0	0.2% (0%, 0.7%)	0.8% (0%, 1.7%)
2–6	1.0% (0.4%, 1.6%)	6% (5%, 8%)
7–13	5% (4%, 7%)	17% (14%, 20%)
14–2	17% (10%, 24%)	45% (35%, 55%)

From Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* 2006;49(3):466–5 [discussion: 475–7]; with permission.

be selected for office-based management. A hypothetical patient presenting with 4 small, LG, noninvasive-appearing recurrent tumors found more than 12 months from the primary resection is a reasonable patient for offering this approach. This patient would have 1-year and 5-year risks of recurrence of 38% and 62%, and progression rates of 1% and 6%, respectively.

Although no prospective work has provided a cutoff of risk stratification at which it is safe to offer office-based management, a suggested treatment algorithm has been proposed by Donat and colleagues²⁴ (Fig. 2). The authors typically offer this strategy to patients who have fewer than 5 recurrent tumors that are smaller than 1 cm, appear to be LG Ta, and have a progression score that puts them in the bottom 2 risk groups (EORTC progression score <7).

PATIENT PREPARATION AND PROCEDURE TECHNIQUE

After appropriately selecting patients based on the previously outlined criteria, the authors discuss the benefits of office-based management, including avoiding an intraoperative procedure and associated morbidity, decreased time commitment, convalescence, and cost. Then, what patients will experience during the procedure is outlined, including distinguishing the procedure from diagnostic cystoscopy, describing the sensation of the cautery device as a light pinprick, and that the

procedure will be stopped at any time if requested. Informed consent is obtained before proceeding.

Prior to the procedure, patients provide a voided urine specimen that is checked with a dipstick urinalysis to ensure there is no sign of a urinary tract infection. Patients are given a single dose of oral antibiotics for urinary tract infection prophylaxis. The authors follow recommendations by Herr and colleagues¹² to obtain a cytology specimen at the time of fulguration to increase the discriminative power of visual inspection for correctly identifying LG NMIBC. If cytology is later found positive for high-grade disease, patients are taken to an operating room for formal TUR and pathologic evaluation. The authors do not routinely obtain tumor fragments for pathology during office-based fulguration because this increases the cost of the procedure and has not proved necessary beyond visual diagnosis and cytology. However, biopsy devices are available for obtaining specimens for those who desire that pathologic information.

Patients are positioned on a procedure table in the supine position for men or low lithotomy for women. The authors typically instill 2% lidocaine gel per urethra. Others administer a lidocaine solution into the bladder with a catheter and allow the solution to dwell in combination with or instead of the urethral lidocaine gel.

The authors use a 17-French flexible cystoscope with a 5-French working port and a camera displaying the image on a monitor at the bedside. Sterile water is used for irrigation and a flexible monopolar Bugbee electrode is passed through the scope to fulgurate tumors. Typically, the coagulation setting is turned to 25 W. The authors begin cauterizing the papillary fronds, move centrally, and finish at the base; the base tends to be more sensitive, and the authors find it better tolerated in this order. Some clinics do not have access to a cautery generator, limiting the ability to perform office-based fulguration. This generator, or even the more expensive holmium:YAG laser generators, may be borrowed from an operating room when needed instead of purchasing a dedicated device for a clinic.

Descriptions of holmium:YAG settings and technique vary and are flexible, depending on surgeon experience and preference. Published series report use of 200- μ m to 550- μ m laser fibers, power settings of 10 W to 40 W (1–2.2 J at 10–40 Hz), and vaporization with or without tumor resection.^{27,29,30}

An indwelling catheter is not routinely left in place after the procedure. Patients are educated on expected findings of bladder spasms, mild hematuria, and irritative voiding symptoms and instructed to monitor for signs and symptoms of

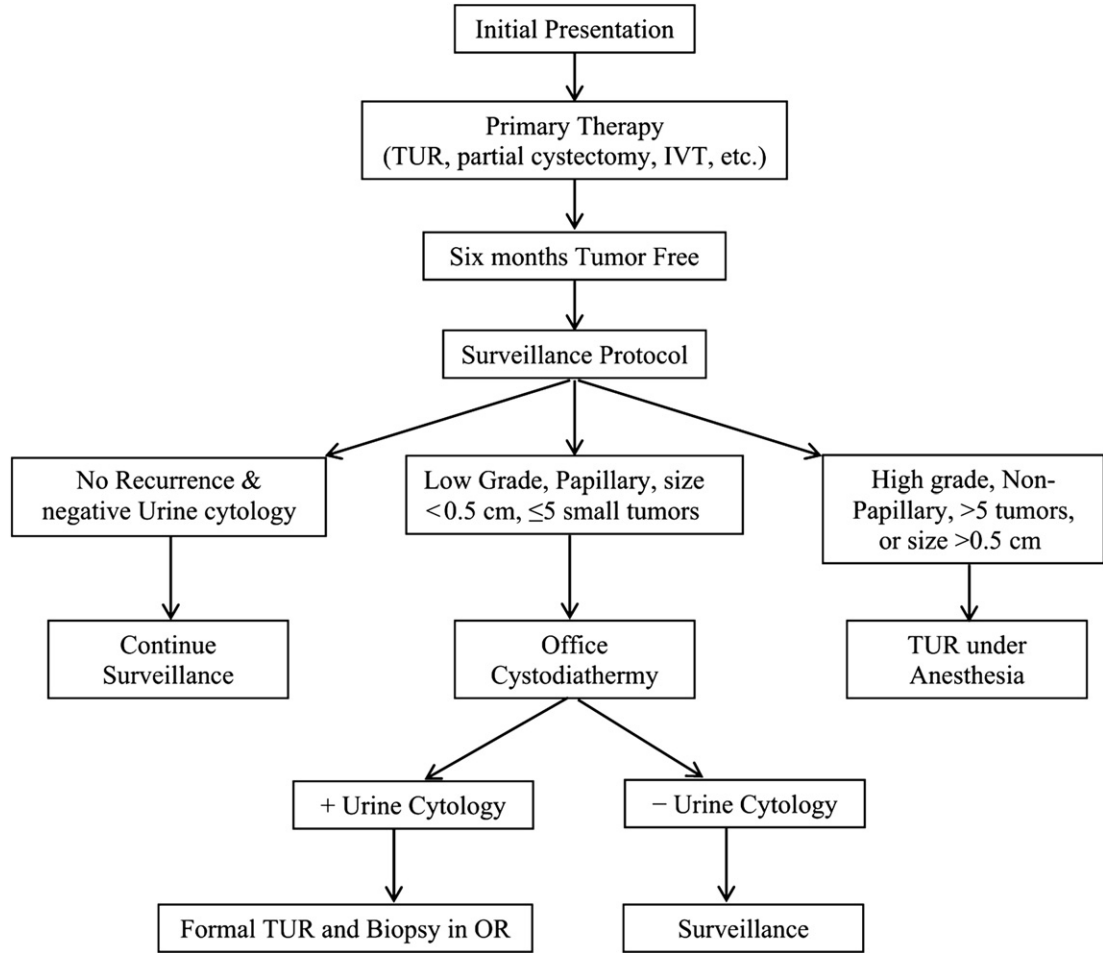


Fig. 2. Treatment algorithm for LG NMIBC. IVT, intravesical therapy; OR, operating room. (From Donat SM, North A, Dalbagni G, et al. Efficacy of office fulguration for recurrent low grade papillary bladder tumors less than 0.5 cm. J Urol 2004;171(2 Pt 1):636–9; with permission.)

urinary tract infections. The authors provide a prescription for a few doses of narcotic pain medication and an anticholinergic for bladder spasms but do not routinely continue antibiotics beyond a single preoperative dose. Patients are required to void before discharge from clinic to minimize the risk of urinary retention at home.

FOLLOW-UP

In the absence of guidance from level I medical evidence, the follow-up schedules for surveillance cystoscopy after treatment of NMIBC tend to be variable. Most agree that a risk-adapted strategy should be used to personalize patients’ follow-up cystoscopies according to their individual risk of tumor recurrence or disease progression. The authors tend to follow patients with LG NMIBC who undergo office-based fulguration in the following manner: history and physical examination,

urine cytology, and surveillance cystoscopy at 3 months; then, every 6 months through 2 years; and then, annually, unless there are tumor recurrences. The National Comprehensive Cancer Network and the European Association of Urology provide further guidelines on surveillance for NMIBC at the following Web addresses: <https://subscriptions.nccn.org/login.aspx>; <http://www.uroweb.org/guidelines/online-guidelines/>.

ALTERNATIVES

An initial expectant management approach has been proposed by other investigators who argue that resection or fulguration is not needed at the initial finding of recurrent lesions in patients with LG NMIBC. Soloway and colleagues³² presented data from 32 patients with a history of resected bladder cancer who underwent an initial observation period after diagnosis of a new lesion.

Criteria for resection included significant growth, change in appearance suggesting grade or stage progression, or hematuria. Mean time observing tumors before operative intervention was 10 months and 3 of 45 observed tumors progressed to high-grade lesions. Eight tumors spontaneously regressed during observation. It is unreasonable to monitor small LG NMIBC lesions before office-based fulguration, but there is a risk that lesions could grow sufficiently to require management in an operating room.

COMPLICATIONS

No reports have specifically addressed complications of office-based fulguration. Rates of early postoperative complications after traditional operative TUR have been reported at 5.1% and include need for reoperation (2.7%), bleeding requiring transfusion (3.4%), bladder perforation (1.3%), and sepsis (<1%).³³ The authors' experience is that there is minimal postprocedure bleeding and they have not had any episodes requiring transfusion or operative/inpatient management for hematuria. Infection rates should approach those of similar endoscopic procedures, and the authors have not had any episodes of bladder perforation.

SUMMARY

LG non-muscle invasive bladder tumors recur frequently but typically have a low progression rate. Prior studies have shown that such tumors may be managed successfully with an office-based treatment approach rather than proceeding to an operating room for a formal TUR. Such an approach likely reduces operative and anesthetic-associated morbidity and cost. In carefully selected patients, office-based management of LG noninvasive bladder cancer is cost effective, well-tolerated, and represents a safe treatment strategy for recurrent LG-appearing bladder tumors.

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Perioperative Chemotherapy

When to Use It, What to Use, and Why

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KEYWORDS

• Bladder cancer • Noninvasive • Chemotherapy • Intravesical • Perioperative

KEY POINTS

- Numerous intravesical chemotherapy agents are available for use in non-muscle invasive bladder cancer with different mechanisms of action and side-effect profiles.
- In the absence of suspected bladder perforation, immediate perioperative dose of intravesical chemotherapy reduces the risk of recurrence for low-grade disease.
- Induction and maintenance therapy is recommended in intermediate-risk disease.
- Intravesical chemotherapy is being investigated as a possible second-line treatment of high-risk non-muscle invasive bladder cancer in patients who are not operative candidates or who refuse cystectomy.

INTRODUCTION

Although transurethral resection of bladder tumor (TURBT) is the gold standard for initial diagnosis and primary treatment of non-muscle invasive bladder cancer (NMIBC),^{1–6} up to 45% of patients will have a tumor recurrence within the first year after TURBT alone and 3% to 15% of patients will have tumor progression.² Tumor cells left in the bladder mucosa after incomplete TURBT as well as free tumor cells that reimplant immediately following TURBT are thought to contribute to the high rate of recurrence. Cytotoxic intravesical chemotherapy is a recommended adjunct to endoscopic resection to reduce the risk of post-TURBT tumor cell implantation and subsequent tumor recurrence, particularly in lower-risk tumors.^{1–6} Instillation of antitumor agents into the bladder allows direct contact with the mucosa and tumor cells and minimizes systemic effects.

A variety of agents are available with distinct characteristics, mechanism of action, cost, and side-effect profile. These agents include mitomycin

C (MMC); thiotepa; gemcitabine; and intercalating agents, such as doxorubicin, epirubicin, and valrubicin (**Table 1**). The cytotoxic ability of the chemotherapy agents is proportional to the concentration of the agent in the bladder and duration of exposure rather than the size of the dose administered.⁷ Absorption, efficacy, and systemic toxicity depend on molecular characteristics, pH during instillation, and time to administration following resection.

Most chemotherapy agents are well tolerated, particularly a single perioperative dose. Local lower urinary tract symptoms, including frequency, urgency, and dysuria, are the most frequently reported side effects.^{2,8} Hematuria, bladder pain, and prostatitis are encountered with similar frequency in all agents. Bladder contracture is a rare event with chemotherapy treatment; and systemic side effects (immunologic reactions, malaise/fatigue, nausea/vomiting, and neurologic, cardiovascular, or pulmonary complications) are less frequently seen than with immunotherapy regimens, such as bacilli Calmette-Guerin (BCG)

Disclosures: None.

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Table 1
Intravesical chemotherapeutic agents

Agent	MW (kD)	Cystitis (%)	Other Toxicity	Dropout Rate (%)	Dose/Concentration	Cost (\$)
Doxorubicin	580	20–40	Fever, allergy, bladder contraction (5%)	2–16	50 mg/50 mL	36
Epirubicin	580	10–30	Contracted bladder (rare)	3–6	50 mg/50 mL	595
Valrubicin	724	23–77	Rash (rare)	—	800 mg/55 mL	4400
MMC	328	30–40	Rash (8%–19%), contracted bladder (5%)	2–14	40 mg/20 mL	130
Thiotepa	189	10–30	Myelosuppression (8%–19%)	2–11	30 mg/30 mL	80
Gemcitabine	300	Minimal	Nausea (rare)	<10	1–2 g/50–100 mL	540–1080

Abbreviation: MW, molecular weight.
Data from Jones JS, Campbell SC. Non-muscle-invasive bladder cancer (ta, T1, and CIS). In: Wein AJ, Kavoussi LR, Novick AC, et al, editors. *Campbell-Walsh Urology*. 10th edition. Philadelphia: Elsevier; 2011. p. 2447–67; and O'Donnell MA. Practical applications of intravesical chemotherapy and immunotherapy in high-risk patients with superficial bladder cancer. *Urol Clin North Am* 2005;32(2):121–31.

and/or interferon. Side effects significantly increase with multiple doses of chemotherapy, which can make completing these regimens difficult.

In clinical practice, significant variations exist in treatment intensity and adherence to best-practice guidelines that tend toward underuse of intravesical therapy.^{9–12} Physician self-reporting suggests that practice setting (private vs academic), years in practice, and tumor grade were associated with deviations from published guidelines.¹³ These variations likely have significant economic as well as oncologic implications that warrant further study and efforts for quality improvement.^{11,13} Clinicians should be informed on the most up-to-date evidence-based guidelines for intravesical chemotherapy for NMIBC.

**CHEMOTHERAPY AGENTS:
CHARACTERISTICS, DOSING, AND ADVERSE
EVENTS**
MMC

MMC is the most frequently used and thoroughly studied intravesical chemotherapy agent for NMIBC (see [Table 1](#)). It is a 328-kD DNA alkylating agent derived from *Streptomyces caespitosus*. It binds to DNA and causes a reductive activation reaction followed by 2 N-alkylations. This reaction results in DNA crosslinking, synthesis inhibition, and strand breakage. Although MMC is cell-cycle nonspecific, it seems to be more active during the G1 and S phases.

Optimal dosing and administration schedule continue to be debated.¹⁴ Dosage varies between

20 to 80 mg per instillation.⁷ Previously, the most commonly used dosing for multidose regimens was 40 mg in 40 mL of saline or sterile water administered weekly for 8 weeks followed by monthly for 1 year.² In 2001, Au and colleagues¹⁵ studied measures to optimize the efficacy of MMC in a phase III randomized trial, which have largely been adopted as the standard of care. Higher drug dose (40 mg vs 20 mg), higher concentration (20 mL vs 40 mL) urinary alkalization (1.3 g NaHCO₃ by mouth the night prior, morning of, and 30 minutes before treatment), a period of dehydration before treatment (no fluids for 8 hours prior), and confirmed bladder emptying before instillation (<10 mL by ultrasound bladder scan) in the treatment arm resulted in increased recurrence-free survival. MMC is more stable in alkaline environments, yet its cytotoxic effect is greater in acidic urine. Whether its increased cytotoxic effect in lower pH outweighs its greater stability at a higher pH is unknown and a potential area for future study.¹⁶ Other methods of optimizing drug delivery, including microwave hyperthermia and electromotive instillation to accelerate drug delivery into and across biologic membranes, have shown promise; but further confirmatory studies are required before becoming routinely used.^{17–20}

Because of its moderately high molecular weight of 328 kD, transurothelial absorption of MMC is minimal. Therefore, systemic symptoms and life-threatening complications, such as myelosuppression, are rare. Bladder contraction and bladder wall calcification are also uncommon to

MMC. Primary complications include chemical cystitis, contact dermatitis, and allergic reactions, which resolve with discontinuation of therapy and topical steroid application if necessary.⁸ A meta-analysis reveals that local complication rate after TURBT with single-dose MMC is approximately 2%, which is comparable with the rate after TURBT alone.² However, the rate of local cystitis increases to 20% to 40% of patients receiving multiple administrations and/or maintenance courses of MMC.^{2,21}

Intercalating Agents

Doxorubicin (580 kD), epirubicin (580 kD), and valrubicin (724 kD) are 3 chemotherapy agents in the anthracycline antibiotic class and are derived from the bacterium *Streptomyces peucetius*. These drugs are DNA intercalating agents, acting primarily by binding to DNA and inhibiting the progression of the enzyme topoisomerase II during DNA replication. The topoisomerase II complex is unable to reseal the replicating DNA double helix, thus resulting in strand breaks and inhibition of essential cellular protein synthesis. The intercalating agents have a broad range of chemotherapy activity, disrupting the cell by several mechanisms, including cell membrane disruption through the production of free radicals. These agents are not cell-cycle specific but have maximal activity during the S phase.

Dosing of doxorubicin ranges from 10 to 100 mg, with a wide variety of administration schedules, from 3 times a week to monthly.²

Increased side effects with doxorubicin, including local symptoms of chemical cystitis in up to 50% of patients, hematuria, and reports of decreased bladder capacity, make this agent a less desirable choice.^{7,8} Systemic side effects are rare because of the high molecular weight of this compound, but occasional reports of life-threatening myelosuppression have been reported.

Epirubicin is a derivative of doxorubicin (4' carbon epimere), differing only in to the presence of a daunosamine side chain. Similar in terms of mechanism of action and efficacy, the different spatial orientation of the hydroxyl group at the 4' carbon of the sugar moiety may account for faster elimination and potentially reduced toxicity. Although epirubicin is approved by the Food and Drug Administration (FDA) for use in various malignancies in the United States, it is only available for use in urothelial cancer in Europe.

Epirubicin has been evaluated as a single perioperative dose and a full 8-week course. Dosing ranges from 50 mg per instillation for weekly dosing to 100 mg per dose with single instillations.^{22,23}

Multiple investigators have demonstrated efficacy of doxorubicin and epirubicin in reducing recurrence but not progression on NMIBC²²⁻²⁷; however, current guidelines make no clear recommendation on the use of these agents for prophylactic chemotherapy because of the side-effect profile, lack of long-term efficacy results, and controversial results.^{1,3-7}

Valrubicin is a semisynthetic analogue of doxorubicin reserved for use in select BCG-refractory tumors.²⁸⁻³⁰ Similar to the other intercalating agents, valrubicin inhibits nucleoside incorporation into nucleic acids resulting in cell-cycle arrest in G2. In addition, the principal metabolites of valrubicin inhibit DNA synthesis through inhibition of topoisomerase II.³⁰

It has several molecular-level differences from doxorubicin, which allows for more rapid uptake and accumulation into cells.³¹ These differences account for valrubicin's decreased contact and cardiac toxicity.³² The fact that valrubicin is a macromolecule explains the lack of systemic absorption and toxicity.

It was previously removed from the market in 2002 because of impurities in the original formulation but reintroduced in 2009 and approved for the treatment of BCG-refractory carcinoma in situ (CIS) in patients who are not candidates for radical cystectomy. Valrubicin is typically administered weekly for 6 weeks at a dose of 800 mg per instillation.³³

Thiotepa

N,N',N'-triethylenethiophosphoramidate (Thiotepa, thiotepa, 189 kD) is an organophosphorous compound that disrupts DNA synthesis and promotes strand breakage through its DNA alkylation activity. This agent is not cell-cycle specific.

Thiotepa is the first and only chemotherapeutic agent specifically approved for intravesical treatment of papillary bladder cancer.³⁴ Although efficacy has been proven through numerous clinical trials dating back to the 1970s,³⁴⁻³⁸ its low molecular weight results in systemic absorption of up to half of the administered dose and a subsequent higher rate of systemic side effects, including myelosuppression and skin rash.⁸ Consequently, the risk-benefit analysis of thiotepa is less favorable than other currently available agents and infrequently used in clinical practice.

Gemcitabine

Gemcitabine (300 kD) is a relatively novel chemotherapy agent. First approved in the United States for the treatment of pancreatic cancer, it is classified as an antimetabolite and has a broad range of

anticancer activity.² Its structure mimics that of cytosine, one of the pyrimidine molecules of DNA.

Phosphorylation of gemcitabine by nucleoside kinases within the cancer cell forms active metabolites (gemcitabine diphosphate and gemcitabine triphosphate), which block DNA synthesis and lead to apoptosis.³⁹

Several pharmacologic properties of gemcitabine are conducive to effective intravesical treatment and support utility in NMIBC. In vitro, researchers have demonstrated a robust cytotoxic effect against cultured bladder cancer cells.⁴⁰ In vivo, low molecular weight and high lipid solubility allows adequate uptake into malignant cells, whereas high plasma clearance reduces the risk of systemic side effects caused by absorption of the drug.⁴¹

Doses of 500 mg, 1000 mg, and 2000 mg in 50 mL saline, instilled for 1 to 2 hours, and administered weekly for 6 weeks have been studied.^{2,42} Recent phase I trials demonstrate a favorable safety profile,⁴³ and several small phase II trials have subsequently reported good tolerability and potential efficacy in tumor response and disease-free survival in certain patient populations.^{42,44–47} Systemic and local toxicities were generally minimal; these studies suggest that dose escalation may be possible, potentially increasing efficacy with a tolerable side-effect profile.⁴²

Despite promising initial efficacy and tolerability data, recommendations on the use of intravesical gemcitabine cannot yet be made given the current available evidence. Variable clinical settings, patient population, trial objectives, and study design limit the current evidence base. Further evaluation by additional phase II and randomized phase III trials in an expanded patient population is warranted and ongoing.^{2,48}

INDICATIONS

Risk Category Definitions

The major guidelines do not uniformly agree on the definition of low-, intermediate-, and high-risk disease.^{1–5} For the remainder of this review, risk categories coincide with the following practical definitions outlined by the International Bladder Cancer Group: low risk is defined as solitary, primary low-grade Ta; intermediate risk as multiple or recurrent low-grade tumors; and high risk as any T1 and/or G3 and/or CIS.⁶

Single Perioperative Dose

A single perioperative dose of intravesical chemotherapy is recommended immediately after initial TURBT in suspected low-risk disease in the absence of concern for bladder perforation.^{1–3,5,6}

The National Cancer Control Network (NCCN) maintains that TURBT alone is the gold standard for low-risk patients but that an immediate postoperative chemotherapy dose should be considered based on the risk of recurrence and progression.⁴ A single instillation at the time of TURBT reduces the rate of recurrence primarily in the first 2 years but does not reduce the risk of progression or survival. This benefit disappears in recurrent, large (>5 cm), high-grade or high-risk patients receiving BCG.⁶ Studies have shown that the combination of negative urine cytology and cystoscopic expertise accurately identifies histologically confirmed low-grade tumors in greater than 90% of cases, which supports the ability of the urologist to predict which patients will benefit from a single instillation of perioperative chemotherapy preoperatively.⁴⁹

MMC is the most frequently administered single-dose agent and is the most widely investigated. Although optimal timing for post-TURBT MMC administration has not yet been determined, improved recurrence outcomes are found only in studies that administer MMC within 24 hours of TURBT.^{50–53} Therefore, single-dose therapy should be administered immediately after TURBT, and ideally within 6 hours, when there is no suspicion of perforation.^{1–6,54}

It is the authors' practice to administer MMC in the following manner. After resection and confirmation of absence of clinical perforation, place a 3-way catheter into the bladder and attach the inflow port to a saline infusion bag while still in the operating room. Administer MMC through the outflow port either in the operating room or in recovery and clamp the outflow tubing with a hemostat. After 1 hour, release the outflow tubing and allow irrigation and drainage to gravity for 30 to 60 minutes. The catheter may then be removed and discarded in a biohazard container. Gloves should be worn at all times when handling this agent.⁵⁴

A 2004 meta-analysis of 7 randomized trials^{22,23,26,38,55–57} compared a single perioperative instillation of intravesical chemotherapy following TURBT versus TURBT alone in patients with Ta or T1 bladder cancer.⁵⁰ Three trials included epirubicin (728 patients, 49.3%), 2 studied MMC (427 patients, 28.9%), and thiotepa (247 patients, 16.7%) and pirarubicin (160 patients, 10.8%) were evaluated in 1 trial each. Chemotherapy was instilled within 24 hours in all trials and generally immediately after or within 6 hours after TURBT. The trials were published between 1985 and 2002 and reported on patients who were accrued between 1981 and 1994. The mean follow-up was 3.4 years (range 2.0–10.7 years).

Recurrence occurred in 36.7% of patients receiving chemotherapy compared with 48.4% in the TURBT-only groups. This finding represented a 12% absolute reduction in risk of recurrence and a 39% decrease in the odds of recurrence within the study timeframe.⁵⁰

There was no difference in the size of treatment effect in the epirubicin, MMC, and pirarubicin trials, although no benefit was observed in the trial using thiotepa, potentially because of the lower concentration used in the included study. It must be noted that this meta-analysis was not designed to determine superiority of a single agent.

Time to realization of treatment benefit varied between the studies, with 3 studies showing a benefit within 1 to 3 months, 1 study showing a benefit within 6 months, and 1 showing a benefit after 1 year. All studied that eventually showed reduced recurrence rate did so within the first 2 years, as previously suggested by Solsona and colleagues⁵⁶ in their trial of single-dose MMC.

The treatment effect was observed in patients with both solitary and multiple tumors; however, the recurrence rate was significantly higher in patients with multiple tumors after a single instillation (65.2% vs 35.8%). This finding suggests that a single instillation alone immediately after TURBT may be suboptimal in this patient population.

The number needed to treat based on this meta-analysis was 8.5 (11.7 TURBTs were avoided for every 100 patients treated with single-dose chemotherapy). The authors suggest that treatment is cost-effective because the cost of a TURBT, anesthesia, and possible hospitalization is greater than 8.5 times that of a single instillation of intravesical chemotherapy.⁵⁰

Notably, in the absence of suspected perforation, a single dose of perioperative intravesical chemotherapy confers no additional morbidity to a TURBT alone.^{2,8}

The American Urologic Association (AUA) Bladder Cancer Guideline Panel performed a meta-analysis focusing on the single-dose instillation of perioperative MMC after TURBT.^{2,3} This analysis is comprised of the 2 studies on MMC included in the aforementioned meta-analysis but differs in that all risk groups are taken into account.^{55,56} Tolley and colleagues⁵⁵ reported a 60% recurrence rate in patients treated with TURBT alone and a 45% recurrence rate in those treated with a single perioperative dose of MMC. Solsona and colleagues⁵⁶ found a statistically significant decrease in the recurrence rate in the MMC group up to 2 years; however, the benefit disappeared at the long-term follow-up of 8 years. A total of 427 patients were included in this meta-analysis. Single-dose MMC immediately after

TURBT was found to decrease the recurrence rate by a statistically significant 17% (95% confidence interval [CI]: -28%, -8%).

Neither meta-analysis revealed a significant difference in disease progression or survival. Therefore, the benefit of a single instillation of perioperative intravesical MMC is limited to a reduction in the risk of tumor recurrence, predominantly in low-risk patients and primarily in the first 2 years.

Despite gemcitabine's encouraging efficacy and side-effect profile in certain applications, single perioperative instillations have not been found to reduce recurrence rates and currently should not be used for this purpose.⁵⁸

Induction Therapy, With or Without Maintenance

Summary of guidelines

Although all guidelines recommend some form of adjuvant therapy for intermediate and high-risk bladder cancer, considerable controversy still exists as to the agent of choice for induction therapy (chemotherapy vs immunotherapy), the interval and duration of induction therapy, and the use and timing of maintenance therapy.¹⁻⁶ The varying definitions of risk stratification between the guideline organizations contribute to the controversy.⁶

The International Consultation on Bladder Tumors recommends a single immediate postoperative instillation of chemotherapy followed by further adjuvant intravesical chemotherapy for less than 6 months for intermediate-risk disease; however, the optimal schedule is not well defined.¹

The AUA recommends an induction course of either MMC or BCG for intermediate-risk disease. Induction courses evaluated by the AUA ranged from a single perioperative dose to weekly instillations for 6 weeks, and no specific induction course was recommended. Despite acknowledging that maintenance therapy with MMC likely reduces the recurrence rate compared with induction MMC only, the AUA identified maintenance therapy as optional and does not define an optimal interval or duration.^{2,3}

For low-grade Ta disease, the NCCN recommends observation, single-dose, or induction intravesical chemotherapy. For high-grade Ta disease, observation or intravesical therapy is recommended. BCG is the preferred intravesical agent; however, chemotherapy is also an acceptable alternative for high-grade Ta. The decision to administer intravesical therapy in patients with Ta pathology is based on factors such as tumor size and number of tumors, which may increase the risk of recurrence and progression. For T1 disease,

adjuvant intravesical chemotherapy is only considered as a second-line treatment after BCG failure. Optimal dosing interval and duration for induction and maintenance therapies are not explicitly stated for either risk group.⁴

For low-risk disease, the European Association of Urology (EAU) recommends a single immediate postoperative instillation of chemotherapy. For patients with intermediate risk disease, the EAU recommends the addition of a minimum of 1 year of intravesical chemotherapy or BCG. Intravesical chemotherapy has no role as a first-line therapy in high-risk disease, including CIS.⁵

Evidence

Uniform superiority in terms of recurrence, progression, and/or survival of one particular intravesical agent has yet to be determined for the treatment of bladder cancer. MMC is widely considered to be the most active and effective of the available intravesical chemotherapy agents, but this perception has yet to be directly proven in a clinical trial. Rather, its superiority is inferred from a lack of any trials demonstrating superiority of any other chemotherapy agent when compared with BCG; a meta-analysis of 3 trials (1066 patients) that suggests MMC with maintenance was superior to BCG induction without maintenance for reducing the risk of recurrence.²

Historically, adjuvant BCG was found to be more effective in preventing recurrence when compared with thiotepa or doxorubicin.² However, subsequent meta-analyses comparing BCG with several different chemotherapeutic agents do not uniformly agree,^{59–61} partly because of inconsistencies in patient populations, treatment schedules, tumor characteristics, and/or institutional variation in outcomes.² Recently, randomized controlled trials have proven equal efficacy between BCG and MMC in both short-term⁶² and long-term⁶³ regimens. Notably, both of these studies include high-risk patients. In addition, no evidence exists to suggest superiority of BCG over MMC in reducing tumor progression in direct comparison analysis.^{21,61,64,65} But a large meta-analysis of more than 4800 patients demonstrated a 27% reduction in progression with BCG plus maintenance versus MMC.⁶⁶

Two randomized trials compared a 6-week course of intravesical gemcitabine with similar BCG schedules with or without maintenance.^{66,67} In patients with primary Ta or T1 disease, gemcitabine was found to have equivalent efficacy in recurrence-free survival⁶⁷ but was inferior to BCG in high-risk groups.⁶⁶ Gemcitabine toxicity was consistently less than BCG and could potentially serve as an alternative to patients with high-

risk disease who are unable to tolerate BCG. In conclusion, there is no direct evidence to suggest superiority of a single chemotherapeutic agent.

Similarly, controversy exists about the utility of additional intravesical chemotherapy as compared with a single perioperative instillation for patients with intermediate-risk bladder cancer.^{1–6} A meta-analysis of 22 trials published in 1995 reported that maintenance chemotherapy was actually less effective than a single postoperative instillation.⁶⁸ Despite no randomized controlled trials directly comparing induction MMC with induction MMC plus maintenance, subsequent meta-analyses contradict this conclusion and suggest that maintenance therapy with MMC significantly enhances recurrence-free survival as compared with induction (either single-dose or short induction course) without maintenance therapy.³ Notably, the decrease in recurrence rate was not observed until at least 2 years of maintenance therapy.⁶⁹ Furthermore, the analysis includes studies that had yet to incorporate modifications of the administration protocol of single-dose MMC that were shown to significantly improve efficacy and have largely been adopted as the standard of care.¹⁵ A more recent randomized trial showed that a group of patients with intermediate- to high-risk bladder cancer undergoing a 6-week induction course with MMC plus monthly maintenance instillations for up to 3 years had significantly higher recurrence-free rates (86.1% [95% CI: 77.9%, 91.4%]) than the group undergoing the same induction course with no maintenance (65.5% [95% CI: 55.9%, 73.5%]).⁶² Again, no studies comparing the effect on progression of maintenance MMC versus induction MMC alone are currently available for analysis; therefore, the effect on progression remains unclear.³

The optimal dosing interval and duration for induction and maintenance chemotherapy is not well defined. Only 2 of the 6 studies included in the 2007 AUA meta-analysis used identical induction and maintenance schedules.^{70,71} The remaining 4 studies used widely variable schedules.^{55,72–74} Results from studies, such as Friedrich and colleagues,⁶² seem to support longer courses (greater than 12 months) of maintenance therapy and call into question the recommendations that limit maintenance chemotherapy to a maximum of 1 year.^{5,75}

In conclusion, there is no consensus on the optimal maintenance dose, schedule, and duration due to lack of sufficient data, but more recent studies suggest an increased benefit to a more prolonged maintenance course.

Secondary/Salvage Therapies: Recurrent and/or BCG-Refractory

Because of the high risk of progressing to muscle-invasive disease, early radical cystectomy is the recommended treatment of BCG-refractory bladder cancer.¹⁻⁶ However, intravesical chemotherapy may have a role in salvage therapy in certain patient populations who are either unable to tolerate or refuse cystectomy.

BCG failure is defined by the EAU as (1) detection of muscle-invasive tumor during follow-up; (2) high-grade NMIBC present at both 3- and 6-month follow-up; or (3) any worsening of disease under BCG treatment, such as a higher number of recurrences, higher T stage or grade, or appearance of CIS despite an initial response.⁵ The International Bladder Cancer Group distinguishes recurrence (reappearance of disease after the completion of therapy) from treatment failure (any recurrence or progression of disease during therapy).⁶

In patients with recurrent disease, the management must take into account previous and current levels of risk as well as previous treatments received.⁶ For select low- to intermediate-risk recurrences, treatment with repeat TURBT, single instillation of chemotherapy, and maintenance chemotherapy or BCG with a minimum of 1 year of maintenance may be considered.⁴⁻⁶ Guidelines uniformly recommend cystectomy as the first-line treatment of patients with an intermediate to high risk of disease progression and a high risk of recurrence or treatment failure.¹⁻⁶ The following discussion outlines the existing data on the use of different intravesical agents in the BCG refractory setting.

MMC

Initial reports of secondary treatment with MMC for BCG-refractory bladder cancer demonstrate a minimal benefit. Only 19% (4 of 21 patients) who crossed over to receive MMC after BCG failure were disease free after 3 years.⁷⁶ A subsequent randomized trial evaluating only recurrent Ta and T1 disease reported more encouraging results with a 61% (33 of 55 patients) disease-free rate at a median follow-up of 3 years.⁷⁷ This trial also studied gemcitabine, however, and concluded that MMC was inferior in terms of both efficacy and tolerability; but it should be noted that only a 4-week induction course was used.

Valrubicin

Valrubicin is the only intravesical chemotherapy agent approved by the FDA for BCG-refractory bladder cancer in patients who are not candidates for radical cystectomy. An initial evaluation of

32 patients, 22 of whom had received prior BCG, reported a 42% complete response rate (negative biopsies and cytology) and a 22% partial response rate (negative biopsies but positive cytology), with a mean disease-free interval of 23 months. Five of the 8 patients (64%) who remained disease free at the time of last contact (12.1–38.5 months after treatment) had previously failed treatment that included BCG.²⁹

A recent phase II/III trial designed to complement the pivotal phase III trial published in 2000³³ on valrubicin in BCG-refractory disease was conducted to further investigate the efficacy and tolerability of valrubicin as an alternative to cystectomy in patients with BCG-refractory CIS.⁷⁸ Although this earlier trial included only patients who had previously failed at least 2 intravesical therapies (including at least one BCG course), the supportive trial additionally included patients who were BCG intolerant or BCG naïve. Both trials, despite the dissimilarity in the patient population, reported an identical 18% complete response rate. This finding suggests that valrubicin may be equally effective in patients with less intensive prior intravesical courses and is consistent with the post hoc analysis of the 2000 trial, which concluded that the number of prior courses or instillations of intravesical therapy did not affect the response rate.⁷⁹

Gemcitabine

Gemcitabine seems to be an increasingly viable option for salvage intravesical chemotherapy for both recurrent and BCG-refractory disease. Reported treatment regimens studied consisted of a 2000-mg dose in 50 mL saline once a week for 6 weeks,^{46,77,80} whereas one trial treated patients with two 3-week courses of 2000 mg in 100 mL administered twice weekly.⁴⁷ Of note, no maintenance therapy was administered in any of these studies.

Addeo and colleagues⁷⁷ reported that a 6-week course of gemcitabine for recurrent Ta and T1 bladder tumors resulted in a 72% disease-free rate after 3 years of follow-up. The reduction in the recurrence rate was significantly higher, whereas toxicity, particularly chemical cystitis, was lower than in the group treated with a 4-week course of MMC. Mohanty and colleagues⁸⁰ reported a 60% (21 of 35 patients) tumor-free rate after 18 months in a similar cohort of patients with Ta or T1 BCG-refractory bladder cancer.

Several more observational studies have evaluated the efficacy and tolerability of gemcitabine as an alternative intravesical treatment in patients who are BCG refractory or BCG intolerant. Oosterlink and colleagues⁸¹ reported a 12-month

recurrence-free survival rate of 75% (18 of 24 patients) in the intermediate-risk subset (Ta-T1, G1-2, multifocal, >3 cm) and 46% (7 of 16 patients) in the high-risk (T1, G3, multifocal, highly recurrent, CIS) subset as defined by the EAU Working Group on Oncological Urology. The regimen was well tolerated, with less than 20% of patients experiencing local side effects.⁴⁶ Dalbagni and colleagues⁴⁷ studied 30 patients (14 with CIS, 14 with T1 ± CIS, and 2 with high-grade Ta) who were refractory or intolerant of BCG and refused cystectomy. Fifty percent (15 of 30 patients) had a complete response and 23% (7 of 30 patients) had a partial response. Recurrence-free survival was 21% after 1 year.

One recently published study reported on 20 patients with high-risk NMIBC with BCG-refractory disease who received a standard 6-week induction course and additional maintenance therapy of 2000 mg/50 mL weekly for 3 weeks at 3, 6, and 12 months. After 15 months, 45% (9 of 20 patients) were recurrence free with a mean time to the first recurrence of 3.5 months. In addition, 45% (5 of 11) of the patients who recurred had disease progression.⁸²

In summary, recent data suggest that gemcitabine is well tolerated and has activity against BCG-refractory bladder cancer. It may also be considered in cases of higher-risk BCG-refractory bladder cancer in patients who are unable to tolerate BCG or who are not candidates for or refuse radical cystectomy. However, until further data are available, intravesical gemcitabine as a second-line agent for BCG-refractory NMIBC should continue to be considered experimental.³⁰

ON-GOING TRIALS

MMC

The Memorial Sloan-Kettering Cancer Center is currently recruiting 220 patients to directly compare optimal doses of MMC (40 mg in 20 mL sterile water) and BCG (81 mg in 53 mL diluent and saline) on cancer recurrence after 2 years. Secondary outcomes include cancer progression and need for radical cystectomy. Both arms will receive an identical induction (weekly instillations for 6 weeks) and a maintenance course (3 weekly cycles at 3, 6, 12, 18, and 24 months) ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00974818) ID: NCT00974818).

Studies to evaluate experimental methods for optimizing delivery of MMC, including preoperative instillation of electromotive MMC ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01149174) ID: NCT01149174) and combined bladder wall hyperthermia with MMC ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00384891) ID: NCT00384891), are ongoing.

Gemcitabine

The Southwest Oncology group has 2 ongoing trials involving gemcitabine. S0337 is designed to evaluate the efficacy of a single instillation of gemcitabine as primary treatment of patients with newly diagnosed or occasionally recurring grade I/II NMIBC and has reached its accrual goal of 340 subjects ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00445601) ID: NCT00445601). For BCG-refractory disease, S0353 is a multicenter phase II trial designed to evaluate the efficacy of an induction and maintenance regimen of gemcitabine. Eligibility requirements include stage Ta (grade III–IV or multifocal), T1 (grade II/III), or CIS and have failed at least 2 courses of BCG. The estimated enrollment is 45 subjects ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00234039) ID: NCT00234039).

Taxanes

Docetaxel and Paclitaxel are two members of the antimicrotubular taxane family that have an effective antiproliferative and apoptotic effect on bladder tumor cell lines in vitro.⁸³ Used in a variety of cancers, including metastatic bladder cancer,⁸⁴ phase I trials have recently demonstrated superior urothelial absorption relative to MMC, with minimal systemic concentrations and an excellent safety profile for intravesical administration.^{85–87}

Efficacy in reducing recurrence and extending the durability of response to induction treatment of select patients with BCG-refractory NMIBC has been suggested by small phase I trials^{88,89} and further investigation is warranted.⁷ Columbia University is currently recruiting patients to a combined phase I and II trial to determine the safety and efficacy of a nanoparticle albumin-bound formulation of paclitaxel ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00583349) ID: NCT00583349).

Apaziquone

Apaziquone is a promising new chemical analogue of MMC approved in 2009 for fast track review status by the FDA for intravesical therapy of NMIBC. Apaziquone is a bioreductive prodrug that is converted into active metabolites by intracellular reductases, which are preferentially expressed in tumor cells. The active metabolites are alkylating agents that form DNA strand breaks, and interstrand cross-links resulting in direct damage to DNA synthesis, similar to MMC.⁹⁰

Preclinical studies have shown this drug to be highly effective in bladder tumor cell lines with possible superiority over MMC and an acceptable toxicity profile, and results of phase II trials in patients with low-grade NMIBC have been encouraging.^{91,92} Two identical, multicenter, prospective,

randomized, phase III trials, each enrolling more than 800 patients with low-grade NMIBC, have been completed and results are pending ([ClinicalTrials.gov](#) ID: NCT00598806 and NCT00461591). These trials will report on the effect on the recurrence rate of a single perioperative dose.

Two identical, randomized, placebo-controlled, phase III trials are actively recruiting to evaluate the safety and efficacy on the recurrence rate of 6 weekly instillations of apaziquone versus placebo after a single perioperative dose ([ClinicalTrials.gov](#) ID: NCT01469221 and NCT01410565). The company Spectrum announced in early 2012 that the 2 trials did not meet the primary endpoint of statistically significant difference of tumor recurrence at 2 years, but other results of these trials are needed before coming to any conclusions about the role of apaziquone as an intravesical chemotherapeutic agent.⁹³

SUMMARY

There are a multitude of different agents available for intravesical chemotherapy for NMIBC with variable chemical compositions, modes of action, and side-effect profiles. Although MMC is the most commonly used agent, no particular agent has been proven to be superior to other agents in randomized trials in terms of efficacy. For low-risk NMIBC, a single perioperative dose of intravesical chemotherapy within 24 hours of TURBT has been proven to be safe in the absence of obvious bladder rupture and effective in reducing the likelihood of recurrence by around 40%. The benefit on progression is yet unproven. Although perioperative intravesical chemotherapy is uniformly recommended for intermediate-risk NMIBC, considerable controversy remains about the agent of choice for induction therapy (chemotherapy vs immunotherapy), the interval and duration of induction therapy, and the optimal use and timing of maintenance therapy. Studies have suggested that additional long-term maintenance chemotherapy has been shown to significantly increase recurrence-free rates. Several new intravesical chemotherapy agents are showing early promise in patients who are BCG refractory and BCG intolerant and may serve as an alternative for patients who refuse or are unable to undergo cystectomy.

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Side Effects of Perioperative Intravesical Treatment and Treatment Strategies for These Side Effects

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KEYWORDS

- Bladder • Superficial • Non-muscle invasive • Complications • Management
- Intravesical chemotherapy • Side effects • Toxicity

KEY POINTS

- Absorption of intravesical chemotherapy agents is dependent on molecular weight, concentration, and lipophilic properties. Absorption may also be influenced by surgical technique.
- Toxicity from perioperative intravesical chemotherapy includes both local and systemic effects. Chemical cystitis, manifesting as urgency, dysuria, and suprapubic discomfort is the most common reported side effect occurring in 3.5% to 25% of cases. Systemic complications are unusual, with rates of myelosuppression generally around 1%. The notable exception is thiotepa due to its small molecular weight.
- Severe local toxicity from perioperative intravesical chemotherapy includes bladder calcification, ulceration, or transmural necrosis, which can lead to perivesical fluid collections. These may occur in the setting of missed perforation or in deep resections.
- Skin eruptions are most common with mitomycin C but can occur with other agents. Although the exact cause has not been elicited, the condition usually resolves with removal of the agent and does not result in significant long-term morbidity.
- The most important measure to prevent complications from intravesical chemotherapy is to withhold the agent in the setting of known bladder perforation. In cases of deep resection or clinical suspicion, cystography should be performed to rule out extravasation before administration.
- Patients with peritoneal signs or severe abdominal pain during instillation should be evaluated and treated promptly for chemotherapy extravasation to prevent long-term complications associated with the necrotizing effects of these agents.

INTRODUCTION

Non-muscle invasive bladder cancer is the most common newly diagnosed urothelial bladder cancer with an extremely high propensity for recurrence. The use of perioperative intravesical chemotherapy is an important modality in the management of non-muscle invasive bladder cancer, particularly to help reduce the risk of

recurrence. Immediate postoperative instillation of cytotoxic chemotherapy has been reported to result in greater than a 39% reduction in recurrence compared with transurethral resection (TUR) alone.¹ Both the American Urologic Association and European Association of Urology Guidelines recommend a single instillation of chemotherapy for patients with low-grade urothelial tumors.^{2,3} These cytotoxic agents have minimal absorption

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when administered into the bladder, and therefore systemic side effects are low. Compared with immunotherapy, there is no demonstrable effect on disease progression but given the known risks of systemic absorption with immunotherapy agents such as Bacillus Calmette-Guérin (BCG), intravesical chemotherapy remains the agent of choice in the perioperative setting for non-muscle invasive urothelial tumors.

In this article, some of the side effects and complications that may be encountered with the administration of commonly used intravesical agents in the perioperative setting and strategies to help manage these toxicities are reviewed. Most of the published data obtained from previous reports have attempted to describe the toxicity associated with induction courses (typically 6 weeks); however, this article highlights the toxicity, side effects, and management of a single perioperative instillation of intravesical chemotherapy.

PROPERTIES AND CONSIDERATIONS OF CHEMOTHERAPIES USED INTRAVESICALLY IN THE PERIOPERATIVE SETTING

There is still ongoing debate with regard to the usefulness of perioperative chemotherapy. Some argue that the recurrences in this patient population are rarely invasive and in most cases they are amenable to office-based fulguration. Nonetheless, if a cytotoxic agent is to be administered in the perioperative setting, the benefits should outweigh the potential risks. With this in mind, there are several factors that may influence the urologists’ choice of a chemotherapeutic agent for intravesical instillation.

One of the first factors to be considered is the risk of absorption of the chemotherapeutic agents, which may result in systemic toxicity. Although some factors affecting absorption may be under the control of the operating surgeon (such as surgical technique and depth of resection), others

are strictly related to the physical properties of the agent. Such properties include molecular weight, concentration, and lipophilicity. Although concentration of cytotoxic agents in bladder tissue is necessary, too much absorption may result in toxic side effects. On the other hand, compounds with poor absorptive qualities achieve lower tissue concentrations, mostly working on the bladder surface. To better define the optimal qualities of cytotoxic compounds instilled in the bladder, Mishina and colleagues⁴ determined that the ideal agent should have a pH between 6 and 7, a logP (partition coefficient) either between –0.4 and –1.2 or –7.5 and –8.0, and a molecular weight of at least 200.

Other factors that may increase absorption include agent dwell time, agent concentration, and bladder wall integrity (ie, bladder perforations).⁵ Therefore, if an intravesical instillation is being considered perioperatively and there is any question of perforation, an intraoperative cystogram should be performed to rule out extravasation. Complications of bladder necrosis, inflammation, fibrosis, and peritonitis have all been reported in cases of missed perforation and are discussed later.

CHEMOTHERAPEUTIC AGENTS USED INTRAVESICALLY

As mentioned previously, there are several cytotoxic agents for use in the perioperative period, some of which remain in clinical trials (Table 1). Each has properties that help to explain its value as an intravesical agent and contribute to potential toxicities. Valrubicin is the only agent with US Food and Drug Administration (FDA) approval for intravesical use, although it is not routinely used in the immediate postoperative setting.

Mitomycin C (MMC) is an alkylating agent that has been used systemically to treat a variety of neoplasms. It has a molecular weight of 334 and

Table 1 Commonly used intravesical chemotherapy agents			
Agent	Molecular Weight	Class	Dose (mg)
Mitomycin C	335	Antibiotic; inhibits DNA synthesis by crosslinking	20–60
Thiotepa	190	Alkylating agent; inhibits DNA synthesis by crosslinking	30–60
Doxorubicin	580	Anthracycline antibiotics; intercalate DNA and inhibit synthesis through several pathways	10–100
Epirubicin	580		
Pirarubicin	625		
Valrubicin	720		
Gemcitabine	299	Cytidine analogue; inhibits DNA synthesis through several pathways	2000

is isolated from the bacterium *Streptomyces caespitosus*. There are several proposed mechanisms of action including inhibition of DNA synthesis by DNA crosslinking and superoxide free radical production.^{6,7} FDA approval for systemic use in a variety of cancers was granted in 1974, although its use as an intravesical therapy is still considered off-label. Bone marrow suppression, manifesting as thrombocytopenia and leukopenia are the most common side effects reported when administered systemically.⁸ Extravasation of mitomycin C when it is being administered intravenously is classically known to cause local tissue necrosis, which can be devastating and require surgical debridement in severe cases.^{9–11} Other toxicities with systemic use include hemolytic uremic syndrome, and effects on cardiac, pulmonary, integumentary, and renal systems.^{12–23}

MMC is the most extensively studied agent in terms of establishing an intravesical pharmacokinetic profile. In an experiment in which dog bladders were instilled with 20 mg in 40 mL saline, tissue concentrations decreased sharply with depth through the mucosal and submucosal layers (50% decrease for every 500 μm). Concentrations at depths less than 2000 μm were at the lowest levels of detection (0.1 $\mu\text{g/g}$) and the plasma concentrations were less than 100 $\mu\text{g/L}$.²⁴ This has also been shown in humans who were administered MMC before cystectomy; a logarithmic decrease in concentration of the agent with increasing depth up to 2000 μm was demonstrated.²⁵ In a study of 18 patients receiving 40 mg of MMC intravesically followed by serial plasma measurements, the maximum systemic concentration was approximately 36 ng/mL with no evidence of bone marrow suppression. The investigators noted that, based on other studies, this systemic concentration is much lower than that obtained when administering intravenous MMC with a concentration of 2.0 $\mu\text{g/mL}$ immediately after injection.^{26,27}

Doxorubicin and Derivatives

Doxorubicin is in the anthracycline class of cytotoxic agents, an antibiotic isolated from *Streptomyces peucetius*. Its proposed primary action is inhibition of DNA synthesis through intercalation, although the exact mechanism is not entirely clear.²⁸ With a molecular weight of 580, its absorption through the bladder wall is minimal. The acute side effects of doxorubicin when administered systemically include bone marrow suppression, gastrointestinal upset, and alopecia. Delayed effects include cardiomyopathy, secondary hematologic malignancies, and hepatic disease. The

current recommended dose for intravesical use ranges from 30 to 50 mg. Previous studies demonstrated that a postoperative instillation of 40 mg in 20 mL of doxorubicin allowed to dwell for 2 hours resulted in 1% of the dose being absorbed and detectable in the plasma at very low levels ($>0.2 \mu\text{g/L}$) in 6 of 8 patients.²⁹

Epirubicin is a derivative of doxorubicin, also with a molecular weight of 580 and minimal systemic absorption. When used systemically, it has been proposed to be as efficacious as doxorubicin but with less associated toxicity.³⁰ It is commonly used in Europe both as an immediate instillation after TUR as well as an induction course.³¹ Detectable levels of epirubicin in plasma can be seen after immediate instillation. Tsushima and colleagues³² obtained blood samples from 10 patients at 30, 60, and 120 minutes after a 1-hour intravesical instillation of either 20 mg/40 mL or 50 mg/100 mL epirubicin. At both concentrations there were detectable levels of epirubicin in plasma (20 mg/40 mL, $<2.0 \text{ ng/mL}$ at 1 hour, then undetectable; 50 mg/100 mL, 4.4 ng/dL at 1 hour, $<3.0 \text{ ng/dL}$ at 2 hours, then undetectable). The low circulating levels found with administration may cause some systemic side effects, although the incidence from previous trials is around 1.3%.³³

Pararubicin and valrubicin are also derivatives of doxorubicin. Plasma pararubicin levels were studied in 20 patients who were given 30 mg of pararubicin intravesically at 2 concentrations for 1 hour after TUR. At all time points, pararubicin concentrations were less than detectable limits (2.5 ng/mL up to 120 minutes). The mean recovery percentage of the agent after draining the bladder was 73%.³⁴ Valrubicin is currently the only FDA approved intravesical agent for use in BCG refractory carcinoma in situ.³⁵ It has also been evaluated as an immediate instillation, although it is currently not approved for this use. Although its molecular weight of 723 is one of the largest of all the intravesical agents, it is highly lipophilic and rapidly absorbed into cell membranes, which could lead to increased absorption.³⁶ Studies evaluating the pharmacokinetics of valrubicin used as an induction course have revealed minimal detectable levels in plasma,³⁷ but in a pilot study of 22 patients in whom it was used in the perioperative setting, the systemic exposure was much higher, especially in cases of extensive resection and bladder perforation.³⁸

Thiotepa

Thiotepa is the oldest agent used for intravesical instillation, with results of a series described as

early as 1961.³⁹ As an alkylating agent, thiotepa produces a cytotoxic effect by DNA crosslinking. Its molecular weight of 189 makes thiotepa the smallest of all agents used intravesically. Previous investigators have shown significant systemic absorption of thiotepa when administered in the bladder. Jones and Swinney³⁹ found that up to one-third of the dose was absorbed in 16 patients treated with an induction course. Lunglmayr and Czech⁴⁰ demonstrated that approximately 20% of thiotepa was absorbed when given in patients with normal urothelium and this increased to near 100% in the setting of injured mucosa from fulguration or resection. Given these findings, thiotepa carries a more significant risk of absorption with resultant bone marrow suppression compared with some other contemporary agents used in the perioperative setting.^{6,41}

Newer Intravesical Agents

Gemcitabine is the newest chemotherapy agent that has been investigated as an intravesical agent in the immediate postoperative and adjuvant settings. Commonly used systemically for invasive and metastatic bladder cancers, this agent has been proposed to be ideal for intravesical use. A cytidine analogue, it has several inhibitory effects on DNA synthesis, including inhibition of DNA polymerase.⁴² It is typically administered in the immediate setting at a concentration of 20 to 40 mg/mL (2000 mg in 50 or 100 mL) with a dwell time of 30 to 40 minutes. In the only prospective randomized trial evaluating the effect of immediate intravesical gemcitabine on recurrence-free survival compared with placebo, patients were managed with continuous bladder irrigation for at least 20 hours after instillation.⁴³ At 12 months there was no difference in recurrence-free survival between the treatment and placebo groups.

Despite the ongoing evaluation of this agent in terms of efficacy, previous studies have shown gemcitabine to be well tolerated when administered in the perioperative setting. Maffezzini and colleagues⁴⁴ demonstrated detectable levels of gemcitabine in plasma after immediate instillation at a concentration of 40 mg/mL in a series of 15 patients. The degree of absorption was dependent on the extent of resection and peak levels were obtained at 15 minutes and were much less than the plasma concentration obtained with systemic administration. Toxicity was low with 1 patient developing grade 2 leukopenia (3000–3900/ μ L). A subsequent phase III trial of 358 patients randomized to placebo or immediate gemcitabine has also demonstrated a low risk of toxicity. Adverse events were similar in both groups

(29.5% gemcitabine vs 26.5% placebo) and the investigators concluded that only about 6% of the adverse events in the treatment arm were likely attributed to intravesical instillation. Of these, post-procedural pain, pyrexia, and alopecia were reported in the treatment group (each 1.2%).⁴³ Cases of myelosuppression were not reported. Investigational studies using gemcitabine are ongoing, including the results of the Southwest Oncology trial, which recently completed accrual, and although the exact role for its use has not been defined, it seems to be safe as an immediate instillation.

Apaziquone is a synthetic analogue of MMC and is being studied in the perioperative period in patients with non-muscle invasive bladder cancer. It requires reduction by the intracellular enzyme deoxythymidine-diphosphorase for cytotoxicity. Because this enzyme has been reported to be increased in bladder cancer cells, this may lead to selectivity and could prove advantageous in terms of efficacy and safety.⁴⁵ A pilot study evaluating the pharmacokinetics and side effect profile showed no detectable levels in plasma and similar toxicities to those reported in other series using MMC.⁴⁶ Docetaxel and paclitaxel are chemotherapy agents that inhibit microtubule depolymerization and are being investigated for intravesical use.

SIDE EFFECTS OF INTRAVESICAL CHEMOTHERAPY

Side effects from perioperative intravesical chemotherapy can be divided into 2 separate entities, local and systemic, both of which can further be described as minor or major. From the previous discussion, it is evident that systemic absorption of these agents is in general low and associated with minimal toxicity. However, local side effects are common but fortunately self-limiting in most cases. The following section discusses the local and systemic side effects that are associated with intravesical chemotherapy as well as treatment strategies to manage them.

The true incidence of both local and systemic side effects with intravesical chemotherapy when applied in the perioperative setting is difficult to assess. Much of the data describing adverse events with intravesical chemotherapy is limited to induction courses whereby patients undergo weekly instillations for variable lengths of time. **Table 2** shows local and systemic adverse events that have been reported in previous clinical trials using intravesical chemotherapy in the immediate postoperative setting. Although the overall toxicity is low, reporting on toxicity among these trials is inconsistent and therefore may be underestimated.

Table 2
Toxicities reported from previous trials using perioperative intravesical chemotherapy for superficial bladder cancer

Series	Agent/Dose	Design	No. of Patients Treated	Local Symptoms	Comments	Systemic Symptoms
Tolley et al, ⁴⁷ 1996	MMC 40 mg	3 arms: (1) Immediate MMC (2) Immediate MMC + induction (3) Control	149	Very low	Delayed healing at resection site in a few cases	None reported
Solsona et al, ⁴⁸ 1999	MMC 30 mg	2 arms: (1) Immediate MMC (2) Control	57	Chemical cystitis 3.5%	No difference in catheterization period or hospital stay between groups	None reported No hematologic changes
EORTC30831 ⁴⁹	MMC 30 mg	2 arms: (1) Immediate treatment (2) Delayed treatment	228/229	Chemical cystitis 6% (both groups)	3.0% required delay or discontinuation in arm 1	Rash, dizziness, malaise 7% (severe 1.8%)
EORTC30832 ⁴⁹	Doxorubicin 50 mg	2 arms: (1) Immediate treatment (2) Delayed treatment	189/188	Chemical cystitis 9% (both groups)	2.2% required delay or discontinuation in arm 1	Rash, dizziness, malaise 7.1% (severe 0.8%)
Mostafid et al, ⁵⁰ 2006	MMC	Single arm	177	Pain 1%	Catheter malfunction in 1 patient resulting in MMC contamination on skin	None reported
Oosterlinck et al, ⁵¹ 1993	Epirubicin 80 mg/50 mL	2 arms: (1) Epirubicin (2) Control	205	Chemical cystitis 11.7%	Skin allergy 1%	No hematologic abnormalities
Ali-el-Dein et al, ⁵² 1997	Epirubicin 50 mg/50 mL	RCT, 3 arms: (1) Immediate treatment (2) Delayed treatment (3) Control	55	Chemical cystitis 22% (mild 16%, severe 6%)		None
Okamura et al, ⁵³ 2002	Pirarubicin 30 mg	RCT, 2 arms: (1) Doxorubicin-THP (2) Control	84	Chemical cystitis 25%		No systemic or hematologic abnormalities
MRC Working Party on Urologic Cancer ⁵⁴	Thiotepa 30 mg/50 mL	RCT, 3 arms: (1) Control (2) Immediate treatment (3) Immediate and induction treatment	379	Chemical cystitis <1%		Fluid retention/edema in 1 patient

Abbreviation: THP, (2''R)-4'-O-tetrahydropyranyl.

Local Side Effects

Administration of cytotoxic chemotherapy into the bladder can induce an array of irritative voiding symptoms including dysuria, frequency, urgency, suprapubic discomfort, gross hematuria, and pelvic pain, which collectively are referred to as chemical cystitis. In some cases, the onset of symptoms is immediate and may necessitate removal of an agent for alleviation. All chemotherapeutic agents can produce 1 or a combination of these symptoms. In a meta-analysis published by Sylvester and colleagues,¹ that included perioperative instillations of epirubicin, thiotepa, MMC, or pirarubicin, the reported toxicity incidence of chemical cystitis was approximately 10%. The effects were described as mild and transient in nature. **Table 2** shows a list of previous clinical trials using immediate intravesical chemotherapy that have information regarding local toxicity.

It is evident from review of the studies that the prevalence of symptoms related to chemical cystitis ranges from 1% to 25%. However, these data should be interpreted with caution, because the different methods of reporting toxicity were inconsistent across these studies. Furthermore, some trials did not even address specific data on treatment toxicity (not shown) and true rates of side effects are likely unknown or underestimated. Nonetheless, no serious events were reported in any of these trials.

Management of Chemical Cystitis

Symptoms of chemical cystitis are usually self-limiting and require no further treatment in the perioperative setting. Agents such as phenazopyridine (pyridium) and anticholinergics can be used in more bothersome cases. Powdered opium and belladonna alkaloids in a suppository form can also be used during instillation to provide relief of spasms and discomfort, and to help with retention of the intravesical agent. Other strategies to help reduce discomfort during treatment include ensuring the bladder is empty before instillation of agent and ensuring meticulous hemostasis at the end of resection to prevent accumulation of blood clots that may occlude the catheter and further exacerbate these symptoms. It is difficult to know whether many of the symptoms of cystitis are related to the intravesical agent or the procedure itself; however, management is the same for both. In addition, anecdotal recommendations of a short course of oral steroids have been advocated as significantly beneficial in alleviating severe cystitis-type symptoms (Chang, unpublished data).

Stoehr and colleagues⁵⁵ described a novel technique in efforts to improve patient comfort during

intravesical MMC instillation. They proposed that some of the pain associated with perioperative instillation resulted from the rigid resistance of a clamped catheter and proposed a technique of maintaining the agent in the bladder without clamping. By elevating the urine bag 1 m above the supine patient, MMC was retained in the bladder by hydrostatic pressure (**Fig. 1**). In a randomized trial comparing this technique with the more traditional method of catheter clamping, they found that pain levels scores were significantly lower with the clampless technique and the mean instillation time was significantly longer (110 min vs 83 min).

In our practice, we make every effort to leave the agent indwelling for 2 hours, although depending on the patient and the amount of resection performed, this is highly variable. Patients who experience intolerable side effects during this period are first examined to ensure there is no evidence of peritoneal signs indicating possible extravasation. If absent, an anticholinergic and an intravenous analgesic are administered for pain control as needed, and in our experience this often results in adequate symptom control. As long as this regimen results in sufficient symptom management, the catheter

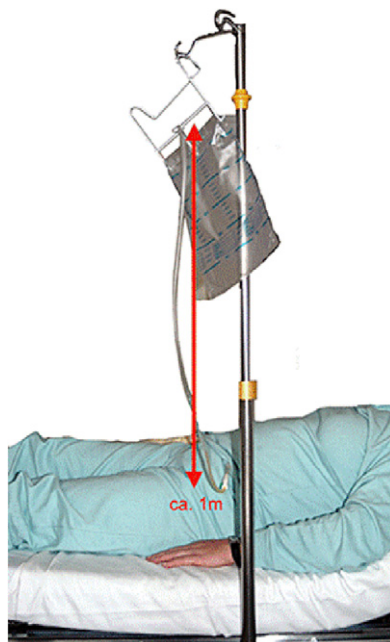


Fig. 1. Technique of maintaining a cytotoxic agent in the bladder through gravity. (From Stoehr B, Mueller T, Granig T, et al. Increasing patient comfort by optimized postoperative administration of intravesical mitomycin C. *BJU Int* 2008;102(11):1556–9; with permission.)

remains clamped with the agent in the bladder. If patient discomfort is not controlled by these measures, then the agent is carefully drained. If any evidence of a clot is present in the catheter at this time, the bladder is irrigated free of clots. In our experience, patients who have undergone large resections, patients with multiple previous resections or intravesical treatments, or patients who have had radiation therapy previously tend to have the most difficulty tolerating perioperative intravesical instillations.

Severe Local Side Effects of Intravesical Chemotherapy

Severe local complications from intravesical chemotherapy have been well described in several case reports. Although the cause is not entirely clear, it is likely that some of these complications occurred in cases of missed extravasation, as cystography was not performed. Examples of these complications include perivesical fat necrosis, bladder ulcerations, necrosis of the corpus spongiosum, fistula formation, perirectal fat necrosis with abscess, and pericystitis.

The necrotizing effects of MMC on the bladder have been described in several series. Doherty and colleagues⁵⁶ reported their findings from 12 patients who underwent radical cystectomy, 6 of whom had previous instillation of MMC or epirubicin. Median time between intravesical chemotherapy and cystectomy was 56 days. On pathologic examination, transmural and extravascular fat necrosis was significantly associated with intravesical chemotherapy supporting the fact that this treatment can lead to necrosis of the bladder wall (**Fig. 2**). Despite these findings, the investigators noted that no systemic or local side effects were encountered during the time of instillation. Branchereau and colleagues⁵⁷ described a case in which a patient developed full-thickness necrosis of the bladder after MMC instillation that ultimately required cystectomy. Thus, not all cases of bladder necrosis occur in the setting of suspected perforation. It has been suggested that cytotoxic agents may be capable of inducing a bladder perforation alone, especially if associated with deep resections of the anterior bladder wall.⁵⁸

Bladder wall ulcerations and calcifications have been reported with intravesical chemotherapy use and may be present for months or years after treatment, and in our experience they are the most common local effect of intravesical MMC administration. In most cases these are asymptomatic; however, concomitant perivesical inflammation has also been reported and

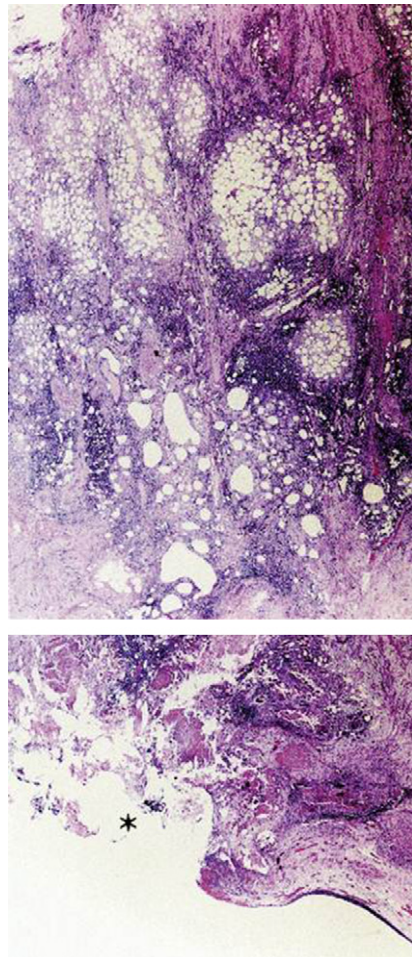


Fig. 2. Hematoxylin and eosin stain under low power magnification of a bladder specimen showing extravascular fat necrosis, fibrosis, and granulomatous inflammatory change. Asterisk indicates the site of TUR. (From Doherty AP, Trendell-Smith N, Stirling R, et al. Perivesical fat necrosis after adjuvant intravesical chemotherapy. *BJU Int* 1999;83(4):420-3; with permission.)

although rare, can cause pelvic pain that can be severe and prolonged in some cases.^{59,60} Caution is advised against performing a biopsy or resection of these areas because they may not heal adequately and thus, as long as these ulcers or calcifications do not change during follow up, we usually do not perform a biopsy or repeat resection.

Treatment Strategies to Minimize Serious Local Toxicity

The risks of severe side effects are conceivably higher in the perioperative setting, due to the compromised integrity of the bladder wall, the

possibility of catheter dislodgement or malfunction from blood clots as a result of recent resection. Extravasation of the agent into the submucosa or intraperitoneal/extraperitoneal space can cause significant damage to the bladder and surrounding tissue, resulting in necrosis, inflammation, and ulceration. Although the incidence of perforations is not entirely clear given the lack of routine cystography, Balbay and colleagues⁶¹ found that extravasation was present in 60% of patients in a series of 35 undergoing tumor resection; larger tumor size was a significant predictor. Thus, the most important factors to reduce the incidence of these side effects is to establish meticulous hemostasis after tumor resection and to perform intraoperative cystography if there is any suspicion of bladder injury. We do not routinely perform cystograms in our patients unless there is clinical suspicion of perforation, but our threshold is extremely low when postoperative chemotherapy instillation is planned. It is also important that the agent is instilled by gravity and if possible while still under anesthesia to minimize patient discomfort with the filling. While the agent is indwelling, it is critical that the nursing staff be familiar with proper techniques for handling and disposing of these cytotoxic agents and remain alert to the warning signs of extravasation or other severe reactions to the agents.

Extravasation when it occurs in the acute setting can be either intraperitoneal or extraperitoneal and typically presents with pelvic pain or abdominal pain out of proportion to what is expected after TUR. If there is intraperitoneal extravasation, involuntary guarding, rigidity, and rebound tenderness consistent with an acute abdomen may be present. If extravasation is confirmed or suspected, the initial management is immediate evacuation of the agent followed by cystography for confirmation. Intraperitoneal perforations rarely heal with conservative measures and in cases where intravesical chemotherapy has been instilled, prompt exploratory laparotomy is required with evacuation of agent and repair of the defect. For extraperitoneal bladder perforations, catheter drainage until the bladder has healed is usually all that is required. We also recommend empirical use of an oral antibiotic for the duration of catheter use because a urinary tract infection in this setting could further complicate healing. A suggested algorithm for management is shown in Fig. 3.

In some instances, bladder extravasation can present in a delayed fashion, days to weeks after instillation (Fig. 4). Presenting complaints may include pelvic or abdominal pain, fever, signs of bowel obstruction, or ileus. Management in this setting involves catheter drainage, but it is also essential to perform imaging to evaluate for fluid

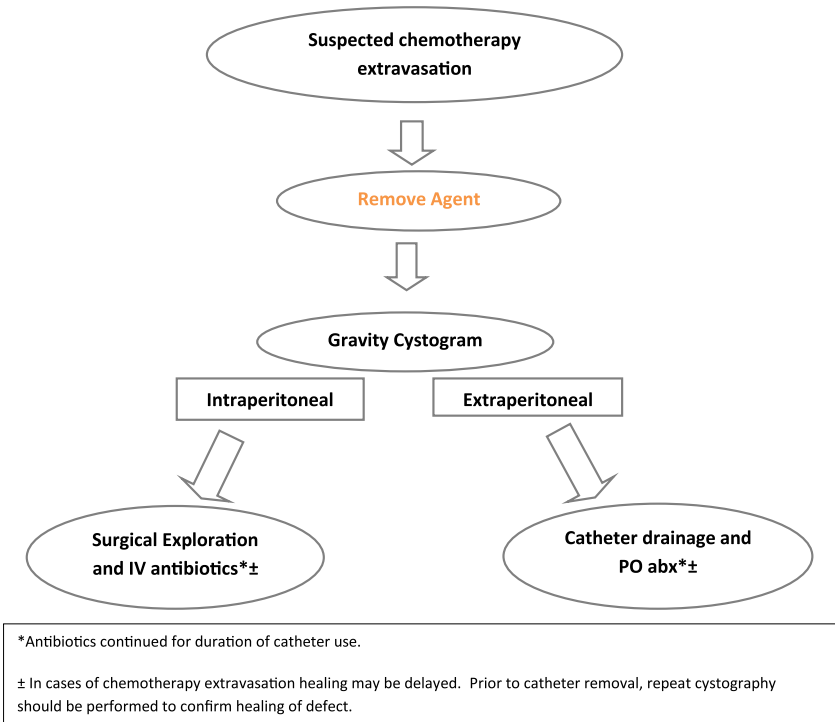


Fig. 3. Suggested algorithm for the management of suspected urinary extravasation during postoperative intravesical chemotherapy instillation.

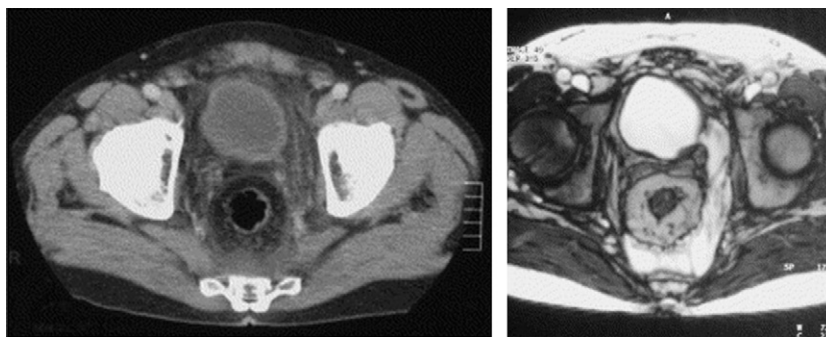


Fig. 4. Patient presenting with persistent pain 4 weeks after postoperative mitomycin C. Computed tomography scan shows bladder wall edema and perivesical stranding (*left*). Magnetic resonance imaging subsequently performed demonstrated left bladder wall perforation with extravasation (*right*). (From Nieuwenhuijzen JA, Bex A, Horenblas S. Unusual complication after immediate postoperative intravesical mitomycin C instillation. *Eur Urol* 2003;43(6):711–2; with permission.)

collection, abscess formation, fistula formation, or bowel obstruction. Several abnormalities have been described including perivesical stranding, extravasation, cutaneous, colovesical, and vesicovaginal fistulae, and the presence of a pelvic mass (typically at the bladder dome) adjacent to the small bowel have all been described.^{62,63} Again, conservative management with catheter drainage of the bladder and percutaneous drainage of fluid collections is the treatment of choice in patients who are stable or do not present with peritoneal signs. When present, fluid collections should be drained and culture-directed antibiotics initiated. When conservative management fails, exploratory surgery is recommended, with excision of necrotic regions and bladder/fistula closure.^{58,60,63} In rare cases, radical cystectomy with diversion may be necessary because of a lack of viable tissue or adequate bladder capacity.^{63,64}

Skin Reactions

Intravesical chemotherapy can cause skin toxicity both by direct contact and by systemic exposure by absorption through bladder epithelium.^{65,66} An estimated 9% of patients develop some type of cutaneous side effect from intravesical chemotherapy affecting both local and distant areas.^{65,67} Although most case reports describing this side effect attribute it to mitomycin C, skin reactions caused by other agents such as epirubicin have also been described.⁶⁸

The exact cause of this side effect is not entirely clear. Colver and colleagues⁶⁵ performed patch tests in 26 patients who had been previously exposed to MMC. They found a correlation between those who had strongly positive tests and those with cystitis (chemical) or skin eruption. Other series have performed patch tests to confirm reaction to MMC and epirubicin that

support a delayed type IV mediated response.^{58,59} Delayed hypersensitivity reactions from exposure to bladder epithelium seem to occur more frequently than direct contamination of skin.^{67,69} Nonetheless, toxicity can develop from either direct spillage or systemic exposure, therefore the urologist must be diligent when using any intravesical agent in the perioperative setting.

Common manifestations of skin reactions include a generalized rash along with dermatitis of the hands and feet or genitalia. Other reported symptoms include eruptions of the face, trunk, or chest, vulvar dermatitis, and palpable purpura of the lower extremities (*Fig. 5*).⁶⁷ There have been 2 case reports describing severe necrotizing reactions involving the glans and ulceration of the penile shaft, which ultimately required total penectomy and perineal urethrostomy (*Fig. 6*).^{70,71} In 1 case, spillage of MMC on the perineum after catheter removal⁷¹ and suspicion of traumatic Foley catheter placement⁷⁰ were attributed as the possible inciting events.

Management of Skin Toxicity

In most cases, cutaneous side effects are self-limiting and resolve after removal of exposing agent. Antihistamines and corticosteroids are useful for those who develop generalized urticaria.⁶ In most of the previous series describing skin toxicity, MMC was used as part of an induction course rather than as a single postoperative dose. If skin reactions develop after exposure in the perioperative setting and considerations are given to additional intravesical chemotherapy, a patch test may be helpful in distinguishing if there is an allergic mechanism present. In those cases, an alternative agent or immunotherapy may be considered in efforts to minimize recurrent reactions.

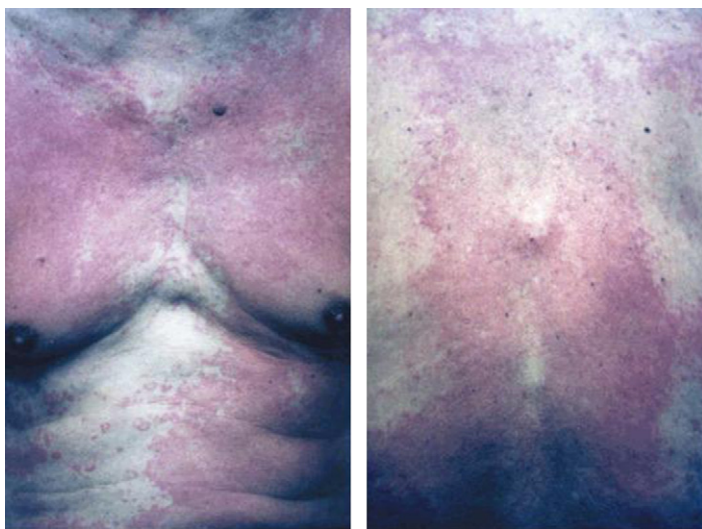


Fig. 5. Drug eruption affecting chest (*left*) and back (*right*) in a patient treated with epirubicin for non-muscle invasive bladder cancer. (Reprinted from Okumura A, Oishi N, Kaji K, et al. Drug eruption due to intravesical instillations of both epirubicin and mitomycin C. *J Dermatol* 2009;36(7):419–22; with permission.)

The patient and caregiver should use universal precautions when handling these agents. Specialized gloves for handling should be readily available and after use, the agents should be disposed of properly. The patient should be instructed to wash their hands and genitalia after the first several voids as residual chemotherapy could still be present. After discharge, it is important that the

patient is counseled regarding signs of local and systemic skin reactions and to notify the physician if any of these unforeseen changes occur.

Systemic Toxicity

Systemic effects of intravesical chemotherapy are rare and primarily result in myelosuppression. Thiotepa is associated with the highest rates of myelosuppression, with leukopenia occurring in 8.4% to 54% and thrombocytopenia in 3.2% to 31% in previous reports.⁶ The induction dose and frequency of administration varied among these series and not all included perioperative instillation.⁶ Another trial using thiotepa in the perioperative setting did not report on rates of myelosuppression.⁵⁴ Soloway and Ford⁴¹ reported their experience of more than 600 thiotepa instillations in 72 patients in both perioperative and induction settings. They found some form of myelosuppression in 18% of cases, which equated to 3.9% of total instillations, but there were no associated adverse outcomes.

MMC has the potential to cause myelosuppression when administered systemically. Given its higher molecular weight, however, systemic manifestations when it is given intravesically are fortunately rare. A review by Thrasher and Crawford⁶ found myelosuppression reported in a total of 8 patients from 3 separate series including more than 150 patients. Multiple other series did not report any evidence of leukopenia or thrombocytopenia. Again, all of these studies involved induction courses after TUR in which patients had repeat instillations up to a year after treatment. Zein and colleagues,⁷² using a single instillation of perioperative MMC at a dose of 80 mg, reported



Fig. 6. Glans necrosis resulting from perioperative instillation of mitomycin C. (From Neulander EZ, Lismer L, Kaneti J. Necrosis of the glans penis: a rare complication of intravesical therapy with mitomycin c. *J Urol* 2000;164(4):1306; with permission.)

a fatal case of aplastic anemia that developed 2 weeks after instillation in a patient with a large resection. However, such reactions are isolated rather than consistent events across series.

The anthracycline agents (doxorubicin, epirubicin, pararubicin) have minimal absorption as previously discussed. Previous trials show the rate of systemic toxicity in the range of 1% (see **Table 2**). A pilot study evaluating tolerability and toxicity of valrubicin in the perioperative setting included 1 patient who developed grade IV neutropenia ($<500/\text{mm}^3$) along with mild anemia and thrombocytopenia.

Other systemic complaints occasionally reported with intravesical chemotherapy include malaise, fever, nausea, and vomiting. Whether these are more related to the procedure itself, the general anesthetic, or from the intravesical instillation is difficult to fully assess.

Management of Systemic Toxicity

Management is usually supportive. Blood products may be given in severe cases of myelosuppression, but the incidence of that is low. At present, the rarity of myelosuppression is such that routine use of laboratory evaluation is unjustified, and routine surveillance of counts is not recommended.⁷³

Long-Term Complications

Intravesical chemotherapy may have long-term effects on the bladder, which may have significant implications. Benign chronic ulcers at the resection site have been described and are attributed to the effect of impaired healing from chemotherapy.^{59,74} These ulcers can pose a diagnostic challenge at surveillance cystoscopy because they can be mistaken for recurrent disease. It is important to use ancillary tests such as urine cytology and fluorescence in situ hybridization in indeterminate situations. These lesions usually heal eventually and only if they change in character or size do we perform a biopsy to rule out recurrent disease.

Calcification or fibrosis of the bladder wall with resulting impaired capacity is another potential long-term complication, and the one most feared by urologists.⁷⁵⁻⁷⁸ The incidence of bladder contracture with use of intravesical chemotherapy is approximately 5%.² Both MMC and epirubicin can cause a reduction of bladder volume and compliance. In a study by Michielsen and colleagues,⁷⁹ the urodynamic changes occurring after MMC and epirubicin instillations were studied in rats. They found a significant reduction in both bladder capacity and compliance that persisted for 3 weeks after treatment. Eijsten and colleagues⁷⁵ found that

long-term results in a series of 75 patients treated with MMC at 2 doses resulted in 6 patients with bladder capacities less than 200 mL. The lasting effects of intravesical chemotherapy can therefore adversely affect urinary function and quality of life. Although prolonged changes of compliance resulting in frequency, urgency, and occasionally incontinence can occur, most patients can be managed with anticholinergic medications with ultimate resolution of these symptoms. In our experience, this may take up to 6 months but more commonly resolve in 3 months.

SUMMARY

Perioperative intravesical chemotherapy remains an important management option for patients with non-muscle invasive bladder cancer. Studies demonstrate consistent reductions in the risk of bladder tumor recurrence. However, the benefits must be carefully considered because patients can experience side effects some of which can be debilitating and even permanent. Many urologists use immediate postoperative intravesical chemotherapy in cases of recurrent tumor when the initial diagnosis is established, and this is certainly a reasonable approach. Proper counseling of patients regarding the risks of intravesical chemotherapy is crucial as well as proper education of operating room and nursing staff to reduce the potential risks associated with administration and handling. When adverse events do occur, early recognition, proper therapy and patient reassurance usually result in satisfactory outcomes.

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Strategies for Optimizing Bacillus Calmette-Guérin

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KEYWORDS

• Superficial bladder cancer • Non-muscle invasive bladder cancer • Bacillus Calmette-Guérin

KEY POINTS

- Bacillus Calmette-Guérin (BCG) is arguably the most effective intravesical treatment option for patients with intermediate-to-high risk superficial bladder cancer.
- A poor understanding of how and when BCG should be used can lead to suboptimal outcomes.
- Careful attention to patient and tumor characteristics can help identify candidates most likely to respond to BCG.
- Specific technical strategies can be employed to optimize BCG outcomes.

INTRODUCTION

As discussed throughout this issue, bladder cancer represents a significant physical and emotional burden to patients as well as a substantial financial burden to society (see the article by James and colleagues elsewhere in this issue). For patients at the extremes of risk, treatment algorithms are relatively straightforward; yet the outcomes are variable. Within the spectrum of non-muscle invasive bladder cancer (NMIBC), for patients with the lowest-risk tumors, the mainstay of treatment is complete transurethral resection (TUR) followed by surveillance (see the article by O'Neil and colleagues elsewhere in this issue); for patients with the most advanced risk tumors, radical cystectomy may be the only viable option (see the article by Daneshmand elsewhere in this issue). Among the areas of greatest uncertainty within the discipline of bladder cancer is the management of patients with NMIBC thought to have a high risk of recurrence and/or intermediate-to-high risk of progression. In this setting, intravesical immunotherapy with bacillus Calmette-Guérin (BCG) is the current gold standard therapy with the highest response rates; however, despite

its frequent use, it remains poorly understood, resulting in usage that is far from optimal.

In this article, the authors review the role that BCG has played in the management of bladder cancer over the last several decades and discuss specific approaches to optimize BCG. They focus on selection strategies to help practitioners identify candidates most likely to respond to BCG as well as on technical strategies to enhance the administration of the drug in such a way as to optimize the response rates, adverse effects, and outcomes (**Box 1**).

HISTORY OF BCG

The history of BCG dates back to the mid-1800s when scientists identified *Mycobacterium bovis* as the causative agent for bovine tuberculosis. Extrapolating from the successful use of the cowpox agent to develop a highly effective vaccine against smallpox in humans, clinical trials were performed in the late 19th century using *M bovis* to prevent tuberculosis in humans. Unfortunately, *M bovis* was proven to be highly virulent in people, and the approach was quickly abandoned.

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Box 1
Strategies for practitioners

Tumor Characteristics

- High-grade tumors with risk of recurrence/progression
- No invasive component
- No aberrant histology (micropapillary, small cell)
- No T1 on prompt repeated TUR

Patient Characteristics

- No active immunosuppression (eg, transplant)
- Elderly okay
- HIV (+) status okay
- Personal history of tuberculosis okay

Technical Aspects

- Give induction + maintenance (SWOG8507 protocol)
- Minimize fluid intake in the hours before instillation
- Start with empty bladder
- Inspect voided urine for visible hematuria (routine urinalysis/dipstick not necessary)
- Catheterize urethra atraumatically
- Minimize lubricant (to avoid BCG clumping)
- Avoid lidocaine (acidity degrades BCG)
- No need for rotisserie-style turning
- Statins/aspirin therapy okay to continue
- Use antispasmodics for local symptoms
- Use antipyretics for influenza-like symptoms
- Give 1 dose of quinolone 6 hours after BCG
- Admit suspected BCGosis/BCG sepsis for prompt workup and aggressive therapy

Several decades later, in 1908, a French bacteriologist, Albert Calmette and a veterinarian, Camille Guérin observed that incubation of *M bovis* in a glycerin-bile-potato medium rendered the bacteria slightly less virulent. Over the next 13 years, they serially passaged the bacteria 231 times, and in 1920 ultimately obtained a strain of *M bovis* that was avirulent in both animals and people.¹ This unique strain came to be known as bacillus of Calmette and Guérin (BCG).

Clinical trials using BCG as a vaccine against tuberculosis were initiated in 1921 but were not met with enthusiasm. Several early catastrophic events caused by cross-contamination with pathogenic strains led to public distrust of the agent. In one particularly disastrous situation in 1930 in Lübeck, Germany, 240 infants vaccinated shortly

after birth all developed tuberculosis, and 72 of these newborns died.² After several decades of disuse, widespread BCG vaccination was once again implemented outside of North America to minimize the postwar increase in tuberculosis expected after World War II. In the United States, BCG vaccination has never been widely adopted.

In the last half century, there has been renewed interest in the application of BCG to the management of patients with various medical disorders. As a potent stimulus of the immune system, BCG has been studied as a treatment option for diabetes mellitus, multiple sclerosis, and Parkinson disease.^{3–7}

In the field of oncology, the first hint that BCG may have a therapeutic role was present in 1929 when Pearl, a pathologist, observed that tuberculosis patients had fewer malignancies than patients who died of other diseases.⁸ In the recent era, BCG has been studied to varying degrees in colorectal cancer, lung cancer, and melanoma.^{9–11} Far and away, the most successful reapplication of BCG in the developed world has been in the field of bladder cancer.

The initial work suggesting a role for BCG within the bladder was performed in 1966 by Coe and Feldman, who demonstrated a consistent and potent T-helper type 1 immune response in pig bladders exposed to intravesical BCG.¹² 10 years later, Morales reported that 9 patients with superficial bladder cancer experienced a decrease in rate of tumor recurrence after intradermal and intravesical treatment with the Armand-Frappier strain of BCG.¹³ This led to a prospective, randomized clinical trial in 1980 that confirmed the beneficial findings of the smaller initial report.¹⁴ In this clinical trial, Lamm and colleagues demonstrated that treatment with a single percutaneous injection followed by 6 weekly intravesical administrations of BCG led to a decreased tumor recurrence rate at 1 year.

Since this initial trial, multiple investigators have undertaken larger trials aimed at more clearly identifying the optimal route, dosing, and scheduling parameters of BCG for patients with superficial bladder cancer.^{15–18} These refinements form the basis of current guidelines concerning the optimal use of BCG in the management of bladder cancer and are discussed further in the following sections. In fact, when BCG is used optimally, it has a definite role in reducing progression and deaths from bladder cancer.^{19,20}

OPTIMIZING PATIENT SELECTION FOR BCG THERAPY

As with all cancer therapies, successful use of BCG is critically dependent on careful patient selection.

For patients with NMIBC, the 2 main indications for the use of BCG are: adjunctive therapy to reduce the recurrence (and progression) of tumors after complete surgical resection of high-grade T_a or T₁ papillary tumors, and ii) primary treatment of carcinoma in situ (CIS).

Tumor Characteristics

For patients with low-grade papillary tumors, BCG therapy is typically not recommended, because, the most patients can be managed with surgical resection (plus or minus single-shot postoperative intravesical chemotherapy) alone. BCG has been used to treat residual tumor in patients with a high volume of disease within the bladder where surgical resection was deemed unachievable and/or for patients medically unfit for any operative procedures with complete response rates up to 66% and partial response rates up to 21%. In general, however, complete endoscopic control is recommended before BCG instillation.^{15,21,22}

For patients with muscle-invasive disease, there is currently no standard role for BCG; the use of BCG or any other intravesical therapy limited to the mucosal surface should be considered insufficient. In 1 report of 13 patients with muscle invasive bladder cancer treated with BCG, only 1 of 13 patients had neither local nor systemic disease recurrence; 10 of 13 patients developed systemic disease, and 7 patients died from metastases.²³ The delay to removal of the bladder that these intravesical therapies impose can have disastrous consequences for patients.

Similarly, for patients with high-risk histologic variants of bladder cancer, BCG therapy may not be sufficient even if the tumors are superficial at diagnosis. For example, in patients found to have micropapillary architecture, the risk of early spread to regional lymph nodes or distant sites is sufficiently high to make conservative local therapy unsafe.^{24,25} For patients with small cell histology or features of neuroendocrine differentiation, the propensity for early microscopic metastases also argues against the use of BCG and other conservative intravesical therapies.²⁶

Given the efficacy of BCG in superficial urothelial tumors and the danger of BCG in muscle-invasive tumors and high-risk histologic variants, it is critical to accurately establish the true stage of any bladder tumor before deciding on therapy. Current guidelines recommend a repeat TUR for all patients with T₁ bladder cancer.^{27,28} This is discussed in more detail by Ritch and colleagues elsewhere in this issue, but the guiding principle before intravesical therapy with BCG should be removal of all cancerous tissue, where feasible.

From the specific perspective of optimization of BCG, data from repeat TUR can help stratify patients into those at higher and lower risk of response to BCG. For example, data from Memorial Sloan Kettering Cancer Center (MSKCC) suggest that patients with initial T₁ disease found to have no tumor or stage less than or equal to T_a on repeat resection have a 19% chance of progression to muscle-invasive disease within 5 years, whereas those patients with evidence of continued T₁ disease at repeat TUR have an 80% chance of progression to muscle-invasive disease within 5 years.^{29,30} While these data are colored with the particular referral biases (and no use of maintenance), it nonetheless provides an impetus to use the repeat TUR data as 1 variable in discussions with patients.

Given the important prognostic information that can be gained from a second TUR, the authors' practice is to perform repeat TUR at 4 to 6 weeks on all patients with T₁ bladder cancer being considered for intravesical therapy. In those patients who have had a complete TUR at the first setting and yet have T₁ disease at repeat TUR (ie, early recurrence of aggressive disease), the authors counsel the patients on the potential high failure rate of BCG and the benefit of early radical cystectomy. However, this does not apply to delayed repeat TUR or repeat TUR where the quality of initial TUR is suspect.

Location of tumor within the bladder may also help predict response to BCG. Tumors located in the prostatic urethra may not have adequate exposure to BCG during instillation and may thus have worse outcomes.³¹ In these patients, it is the authors' practice to perform a limited TUR of prostate several weeks before initiation of BCG to facilitate surface contact of the medication with the urothelium of the prostatic urethra.

Patient Characteristics

Aside from staging and histologic concerns, patient selection must also be optimized. Because BCG is a live attenuated bacterium that exerts its effects primarily via a T_H1-driven response, the patient's immune status is highly relevant. Patients on active immunosuppressive medications following organ transplantation should be considered for BCG therapy only in select cases. Besides the risk from an infective viewpoint, the intense immunostimulatory cytotoxic response evoked by BCG may place the transplanted organ at risk of rejection.

Patients who are very elderly or have poor performance status may have weakened immune systems, but they are still eligible to receive BCG.^{32,33} Although this immunosenescence is

not a contraindication to BCG therapy, it may blunt the ability of BCG to evoke a sufficient immunostimulatory response. Patients with a history of human immunodeficiency virus (HIV) infection can usually also be safely treated with BCG. Given that most patients with HIV in the current era have intact immune systems, their bladder cancer can be managed the same as other patients, and similar outcomes can be expected.³⁴

Lastly, some practitioners mistakenly exclude patients with a personal history of tuberculosis from consideration for BCG therapy. Although there are no data specifically examining this, the authors and others have successfully treated these patients with BCG therapy. In fact, recent data suggest that pre-BCG priming enhances the response of patients.³⁵ However, given the prior exposure of these patients' immune systems to mycobacterial antigens, clinicians should be particularly vigilant about optimizing delivery with respect to the reduction of adverse effects.

OPTIMIZING ADMINISTRATION OF BCG

Although proper patient selection and use of maintenance therapy can improve overall outcomes with BCG therapy, there are also specific strategies in the administration of the drug that can increase the likelihood of successful intravesical treatment. The following paragraphs discuss aspects that can contribute to enhanced outcomes for patients treated with BCG therapy.

Strains

From the initial avirulent strain of *M bovis* cultured by Calmette and Guérin in 1920, multiple sub-strains of BCG have been isolated, and they have been used clinically to varying degrees. These BCG substrains are generally classified as either evolutionarily early (eg, Japan, Moreau, and Russian) or evolutionarily late (eg, Connaught, Danish, Glaxo, Phipps, and Tice). While the early and late substrains are known to be genetically distinct, the exact differences in antitumor activity, if any, remain unknown.

The wide geographic variation in success rates seen with large-scale clinical trials of BCG vaccination for tuberculosis has been postulated to be due at least in part to the variable clinical efficacy of different BCG substrains available locally around the world.^{36–40} In bladder cancer, recent preclinical investigations suggest that immunomodulatory potential differs between the various BCG substrains, but the clinical impact of these differences remains undefined.^{41,42} This should be kept in mind when comparing the results of

clinical trials of BCG in bladder cancer that have used different substrains of BCG.

Dosing

As with other avirulent bacteria prepared for therapeutic use, the dosing measure of BCG is the colony-forming unit (CFU). CFU varies from strain to strain, and a vial of BCG may contain variable amounts of BCG CFU based on lot date, manufacturer, and other factors. Current data suggest that an intravesical dose between 10^8 and 10^9 CFU is effective, but response has been reported with doses as low as 10^6 CFU. These variations explain the differences in recommended milligram dose between different preparations of BCG (eg, Sanofi-Pasteur 81 mg; Tice, 50 mg; Tokyo, 40 mg; Dutch [RIVM], 120 mg).

Duration

The first randomized trial of BCG therapy for bladder cancer examined the efficacy of a treatment regimen that consisted of 6 weekly intravesical instillations of BCG.¹⁴ Subsequent trials have investigated the effect of additional instillations given to boost the immune response. The initial 6-week treatment regimen is known as induction, and the subsequent instillations are referred to as maintenance therapy. In a large-scale cooperative group trial performed in the United States, Lamm and colleagues¹⁸ demonstrated that routine use of BCG maintenance therapy given as 3 weekly instillations at the 3-, 6-, 12-, 18-, 24-, 30- and 36-month time points decreased both recurrence and progression rates for patients with NMIBC when compared with patients who received induction BCG therapy alone. A European intergroup trial published in 2010 found that routine use of this same 3-week BCG maintenance regimen resulted in improved time to recurrence, disease-specific survival, and overall survival when compared with patients receiving intravesical chemotherapy.¹⁹ While future studies will likely continue to elucidate the specific details of the ideal maintenance regimen, the data currently available all suggest routine incorporation of maintenance therapy (using the SWOG 6+3 regimen) if BCG is to be used optimally.

Technique

It is important to optimize the administration of BCG in such a way that the bacterium has optimal propensity to adhere to the urothelium while at the same time causing the patients the least inconvenience/discomfort. In the authors' practice, patients presenting for treatment are instructed to minimize fluid intake in the hours before their

scheduled BCG instillation and to empty their bladders immediately before BCG instillation. The voided urine specimen is visually inspected to confirm absence of gross hematuria (microscopic hematuria or positive dipstick is not a contraindication to BCG). BCG mixed in 50 mL normal saline is then instilled intravesically via a urethral catheter. Minimizing fluid intake and starting with an empty bladder increase the likelihood of successful retention of the medication for the recommended duration of 2 hours. Other technical tips include minimal use of lubricating jelly (to avoid clumping of bacteria), avoidance of lidocaine (the acidic composition can be deleterious), and, of course, to perform the instillation only in the setting of atraumatic catheterization.

An interesting practice among some urologists is to have patients lie recumbent during the instillation period and to have them rotate every 15 minutes in an attempt to evenly expose the entire bladder surface to BCG. Although well-intentioned, this rotisserie method does not seem to have any basis in the scientific literature. The elastic nature of the compliant bladder suggests that it changes size to accommodate the volume of fluid inside. Therefore, unless the instillation was incorrectly done and a large air pocket was introduced in the bladder, serial turning of the patient is not necessary. It is the authors' practice to have patients lie recumbent for several minutes after instillation of the BCG and then to allow them to ambulate normally during the 2-hour retention period.

Usage of certain medications has been suggested to be a relative contraindication for BCG therapy. Because of the increased propensity for hematuria while on antiplatelet agents such as aspirin or clopidogrel, patients taking these medications are sometimes not considered candidates for BCG therapy or are instructed to discontinue the medications during BCG therapy. Similarly, given the documented ability of statin medications to induce a T_H2 immune response (and therefore limit the ability of BCG to induce a T_H1 response), it has been suggested that patients discontinue statins during BCG therapy.⁴³

The authors believe the risk of treatment-altering hematuria due to antiplatelet agents and the risk of immune steal due to statin therapy are both extremely low. There is even evidence to suggest that aspirin therapy may have a beneficial effect on the efficacy of BCG.⁴⁴ Similarly, since the initial report suggesting the negative effect of statin therapy on BCG efficacy, multiple authors have reported no impact of statin therapy on post-BCG outcomes.^{45,46} It is the authors' practice to have patients continue their usual medications during

BCG therapy. The authors generally do not initiate new medications or discontinue ongoing medications in most patients.

Reduction of Adverse Effects

A common misconception around the administration of BCG is that it is too toxic, and practitioners will often quote the data from the SWOG8507 study and cite that "less than 18% of patients finished 3 years of BCG."¹⁸ Although this is true of that study, it must be recognized that these were results from 2 decades ago, and much has been learned since then about optimal administration of BCG. In fact, now, a diligent practitioner should be able to reduce the BCG discontinuation rate in their patients to less than 15%. This has been borne out by the large-scale study⁴⁷ in which less than 10% of patients receiving a full dose therapy for 3 years discontinued BCG because of toxicity. This section discusses the spectrum of adverse effects that may result from BCG and provides strategies to minimize these effects. Most of these side effects can be prevented or managed with minor interventions without the need for termination of BCG therapy. However, the most serious adverse effects demand immediate recognition and prompt initiation of aggressive measures.

Irritative voiding symptoms (dysuria, frequency, and urgency) and low-grade fever are the most commonly reported complaints immediately after BCG instillation.⁴⁸ In most cases, these resolve within 48 hours and do not need intervention. Many practitioners anecdotally regard the transient local symptoms and influenza-like symptoms as an encouraging sign of the intended immune activation effects of BCG therapy. Antispasmodic medications and over-the-counter antipyretics can be used with good effect to control the symptoms. In the authors' practice, patients who experience moderate or severe irritative voiding symptoms are prescribed antispasmodic medication for the acute episode, and they are also instructed to take the antispasmodic medication before subsequent BCG administrations.

The most serious adverse effects with BCG therapy are seen when the medication is inadvertently absorbed into the bloodstream. This allows the *M bovis* bacteria to access the systemic circulation. Depending on the amount of BCG absorbed and the extent of previous immune priming (eg, personal history of tuberculosis), the sequela of systemic BCG spread can range from prolonged pyrexia (BCGosis) to a severe systemic inflammatory response syndrome (BCG sepsis) to death.⁴⁸ Given these dangerous possibilities, it

is imperative that practitioners employ all means to prevent systemic BCG absorption. For this reason, BCG administration should be postponed for any patient with visible hematuria. For patients with a history of tuberculosis, the authors also routinely perform urine dipstick to assess for microscopic hematuria, as absorption of even small amounts of BCG can incite a cytokine storm from the hypersensitized immune systems of these patients.

In all patients, urethral catheterization should be performed as atraumatically as possible, and BCG administration should be postponed if bleeding is triggered during catheterization. BCG should not be given in the presence of a urinary tract infection. During an episode of urinary tract infection, the risk for BCG intravasation is greater. This is because the urothelium is more permeable, and the surface vasculature is predisposed to bleeding more readily. For the treatment of urinary tract infections in patients receiving intravesical BCG, it was previously suggested that use of quinolone antibiotics was to be avoided because of their antimycobacterial activity.⁴⁹ More recently, several investigators have shown that short-term administration of a quinolone decreases the incidence of moderate-to-severe adverse events (especially grade 3 events) after BCG instillation.^{50,51} For this reason, it is the authors' practice to instruct all patients to take 1 dose of a quinolone antibiotic 6 hours after BCG instillation. In the authors' experience, this practice increases patient comfort and decreases the likelihood of patient dropout from BCG therapy.

FUTURE DIRECTIONS

The integration of BCG into the management of patients with superficial bladder cancer has been among the most important advances in the field over the past several decades. Based on the results of multiple large-scale clinical trials conducted in the United States, Europe, and Asia, BCG therapy is now accepted as having a clear role in reducing recurrence, progression, and death from bladder cancer.

In the coming decades, the authors anticipate there will be increasing emphasis on developing accurate predictors of response to BCG therapy. Although several algorithms based on clinical parameters have been developed,^{52,53} the recent acceleration in technologies for gene expression profiling suggests that future efforts will focus on developing molecular markers that predict BCG sensitivity and that allow for personalized cancer therapy. Multiple avenues are being investigated for use as potential molecular biomarkers of BCG sensitivity. These include tumor-associated markers (pRb, CD68, Bcl-2, Bax markers of gene

expression and methylation), urinary markers (interleukin [IL]-2, IL-8, IL-18, tumor necrosis factor- α) and serum markers (single nucleotide polymorphisms in multiple DNA repair, inflammation, cell cycle, and apoptosis pathways).^{54–57} At MD Anderson, the authors have recently performed a prospective clinical trial investigating the concept of molecular recurrence using fluorescence in situ hybridization to predict response to BCG therapy.⁵⁸ The authors are hopeful that this approach may help counsel patients undergoing BCG therapy, and it may also provide a role in future clinical trial design.

SUMMARY

For the treatment of patients with superficial bladder cancer and a moderate-to-high risk of tumor recurrence or progression, intravesical BCG has been the key development of the last generation because of its ability to decrease tumor recurrence, progression, and death from bladder cancer. However, because of its bacterial composition and its intravesical route of delivery, BCG has also brought with it a novel set of challenges that require thoughtful planning and vigilant monitoring. An understanding of when, to whom, and how BCG should be given is critical if optimal outcomes are to be achieved. As the ability to better select patients for BCG therapy continues to be refined in the future, outcomes with this unique treatment will only continue to improve.

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New Agents for Bacillus Calmette-Guérin-Refractory Bladder Cancer

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KEYWORDS

- Non-muscle invasive bladder cancer • Bacillus Calmette-Guérin failure
- Bacillus Calmette-Guérin refractory • Intravesical therapy • Salvage agents

KEY POINTS

- BCG is the most effective treatment for non-muscle invasive bladder cancer, yet roughly 50% of patients still experience tumor recurrence (BCG failures).
- Radical cystectomy is recommended for BCG failure by the AUA and EAU, because no other local therapy has proved as effective at providing oncologic cure.
- Multiple salvage agents have been or are currently under investigation, including intravesical chemotherapy, drug delivery enhancement technology, immunotherapy, and targeted therapies, with varying success rates.
- Despite ongoing research on promising therapeutic approaches, it remains difficult to counsel and treat patients with BCG failure, particularly those who cannot tolerate or refuse radical cystectomy.

INTRODUCTION

An estimated 73,510 individuals will be diagnosed with bladder cancer in the United States in 2012.¹ Roughly 70% will initially be diagnosed with non-muscle invasive cancer (Ta, T1, or carcinoma in situ [CIS]) at presentation; treatment includes transurethral resection (TUR) and possible adjuvant intravesical therapy. The remaining 30% with muscle-invasive disease have a worse prognosis, and a different treatment course, which may include radical cystectomy, systemic chemotherapy, radiation, or any combination of the above. For patients with non-muscle invasive bladder cancer (NMIBC), the aim is to prevent tumor recurrence, which occurs in 50% to 90% of patients at 5 years, and most importantly, disease progression to muscle

invasion, which occurs in up to 20% of patients.² The risk of recurrence and progression is related to multiple factors, including tumor grade, stage, presence of CIS, and multifocality.^{3,4}

Intravesical bacillus Calmette-Guérin (BCG) treatment was first described in 1976, and is currently the standard of care for patients with high-grade NMIBC and CIS.^{5,6} BCG reduces cancer recurrence by 40%, compared with TUR alone, and also reduces progression, unlike other intravesical agents.⁷ Although BCG is the most effective treatment, roughly 50% of patients still experience a recurrence within 5 years.⁸ With each BCG failure, the risk of progression rises; failing two or more courses of BCG increases the risk of developing MIBC from 7% to 30%.⁹

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DEFINING BCG FAILURE

Currently, there is no standardization of terminology for defining BCG failure. In 2003, Herr and Dalbagni¹⁰ published data from a prior trial evaluating the use of BCG maintenance, and analyzed 93 BCG-naïve patients with high-grade NMIBC who then underwent BCG induction. Fifty-one percent of patients were randomized to receive monthly maintenance BCG. At 3-month follow-up, 43% had presence of tumor; by 6 months, only 20% had persistent or recurrent tumor, suggesting a possible prolonged or delayed immunotherapeutic effect of BCG. Long-term tumor recurrence rates correlated only with the presence of tumor at 6-month evaluation, and not with the presence of tumor at 3 months, nor the use of maintenance therapy. As a result, they proposed that patients should not be considered BCG refractory until at least 6 months of follow-up.

In 2005, the International Consensus Panel on T1 bladder cancer aimed to better describe BCG failure by offering four classifications.¹¹ “BCG-refractory disease” was defined as persistent or rapidly recurrent disease at 6 months after induction, despite maintenance or repeat induction at 3 months. Any worsening of stage, grade, or tumor burden at 3 months was also included in this definition. If disease is persistent or recurrent at 3 months, but is nonexistent at 6 months, regardless of TUR status, the patient is considered “BCG-resistant,” indicating that they do respond to BCG, but not as robustly as a complete, immediate responder. The third category is “BCG-relapsing disease,” describing patients who are disease-free at 6 months, but ultimately recur, either early (before 12 months), intermediate (12–24 months), or late (>24 months). The fourth and final classification is “BCG-intolerant disease.” This refers to those who cannot tolerate a full course of BCG, secondary to drug toxicity or a serious adverse event, and have recurrent disease in the face of incomplete treatment. These four definitions encompass all patients for whom BCG does not provide a complete cure, yet unfortunately these categories can overlap, because a given patient could have BCG-resistant disease, but then ultimately have a late recurrence, thus classifying the individual as a BCG-relapser. There are also variables in how patients are managed, particularly in the use of maintenance, dose reduction, follow-up, and preference in the use of salvage therapies and timing of cystectomy. In addition, the thoroughness of cystoscopic surgical resection is difficult to control for across all these categories and can contribute substantially to disease-free status in patients with high-grade Ta, or T1 bladder

cancer.¹² Therefore, standardizing this complicated group of patients would be valuable for assessing prognosis and treatment outcomes.

To this end, Shirakawa and colleagues¹³ retrospectively applied the previously mentioned BCG failure definitions to a cohort of 173 patients who failed BCG as treatment of NMIBC to assess their prognostic validity. Significant risk factors for stage progression (defined as muscle invasion or distant metastases) included BCG-refractory disease versus the other three subtypes, and grade 3 histology at time of BCG failure. BCG-refractory patients also had significantly lower disease-specific survival as compared with the BCG-relapsing and BCG-intolerant groups. Interestingly, only 3 of 173 patients were classified as BCG-resistant. Fourteen percent of patients experienced stage progression, at a mean time of 2.4 years from BCG failure. Intuitively, it seems that BCG-refractory disease should have worse outcomes than BCG-relapsing disease, but validating this is important, as this group attempted to do. The retrospective nature of the paper, along with different treatment protocols, including various other intravesical agents, and a significant number of Grade 1 to 2 Ta tumors, makes it difficult to interpret and to generalize. This investigation does further clarify that standardization of subtypes in this disease state and validation of the outcome research in this population are still needed to better assist clinicians in making appropriate treatment decisions in this group of high-risk patients.

STANDARD TREATMENT OPTIONS

Repeat Induction

On failing one course of BCG, a second BCG induction course can result in a significant response rate.¹⁴ Brake and colleagues¹⁴ examined 126 patients with T1 disease who underwent induction BCG, 37 (29%) of whom recurred at a median of 16 months. The 24 subjects with non-muscle invasive recurrence underwent a second 6-week induction course of BCG, with a 79% response rate (19 of 24) at a median of 24 months, displaying the benefit of repeat induction at time of recurrence. However, 13% of patients (17 of 126) developed progression to MIBC, either after one course (N = 13) or two courses (N = 4) of BCG. There was no placebo group in this study, so it is impossible to know the true effect of second BCG induction as compared with TUR alone. In addition, patients with residual tumor after repeat induction went on to cystectomy; thus, it is unknown if they would have achieved a delayed response, as is seen with primary BCG induction.

Maintenance

Another form of additional BCG is maintenance therapy, as reported in the pivotal randomized trial conducted by the Southwest Oncology Group (SWOG) in 2000.¹⁵ Patients with BCG-naïve NMIBC were randomized to receive intravesical and percutaneous BCG for a 6-week induction course, or induction plus 3 weeks of maintenance at 3, 6, 12, 18, 24, 30, and 36 months. Five-year recurrence-free survival was significantly higher in the maintenance group (60% vs 41%), although there was no significant difference in overall survival. A subset analysis of patients with CIS also showed an improved response rate with maintenance. However, only 16% of patients randomized to maintenance received all 3 years of therapy because of a combination of recurrence and adverse events.

A more recent follow-up review of the SWOG BCG maintenance trial evaluated potential risk factors for recurrence and progression.¹⁶ Early and late (>12 months) recurrence were associated with increased risk of death, compared with no recurrence, but the timing of recurrence was not found to significantly correlate with survival. Of the 394 patients who were disease-free after induction BCG and thus randomized, 185 ultimately recurred and 37 went on to cystectomy, with a 5-year survival rate of 56% for greater than or equal to T2 disease, and 95% for less than or equal to T2 disease. Patients in the maintenance arm were more likely to undergo early cystectomy, at a median time of 11 months versus 24 months, although the rates of cystectomy for MIBC were similar (45% vs 49%). These data provide further evidence that those who recur after BCG, whether early or late, have worse survival than patients who have complete responses (CRs).

Cystectomy

It is difficult to determine exactly when and how to treat a patient who fails BCG. Guzzo and colleagues¹⁷ examined a cohort of 184 patients with cT1 or CIS who underwent cystectomy (64% with prior BCG). Nineteen percent (35 of 184) of patients were upstaged to pT2, and when compared with a group of cT2 who underwent cystectomy (and found also to be pT2), recurrence-free survival rates were lower at 3 and 5 years (64% and 61% vs 83% and 74%). Prior BCG therapy with subsequent upstaging was found to be a risk factor for long-term recurrence compared with patients with known MIBC, highlighting that BCG failure portends poor outcomes, even despite cystectomy.

Delaying radical cystectomy has been shown to increase the risk of death, which can be disconcerting to those receiving BCG, because several

weeks of treatment typically elapse before response to therapy is assessed.^{18–20} Herr and Sogani²¹ showed that in BCG-failure patients, cystectomy within 2 years of initial BCG provided improved 15-year disease-specific survival compared with patients who had cystectomy at least 2 years after BCG (69% vs 26%; $P = .003$). Reviewing two historical cohorts in which different treatment paradigms were used, Raj and colleagues²² compared early (at T1 recurrence) with late cystectomy (at progression to MIBC) in BCG-failure patients. Although retrospective and not randomized, it showed a trend toward improved progression-free and cancer-specific survival in the early cystectomy cohort.

Conversely, Badalato and colleagues²³ reviewed a more contemporary series of 349 patients with high-grade T1 bladder cancer, and showed that immediate cystectomy (within 90 days of diagnosis and without further TUR or intravesical therapy) did not offer a benefit in cancer-specific survival, as compared with conservative therapy. In the more recent subgroup (2000–2010), only 56.7% went on to cystectomy after attempted conservative treatment. Although retrospective in nature, this analysis suggests that delaying cystectomy may be a feasible option to consider.

The American Urological Association guidelines currently recommend radical cystectomy as first-line therapy in patients who fail BCG. The European Association of Urology guidelines state that a patient has failed BCG when a patient develops MIBC, or when high-grade NMIBC is present at both 3 and 6 months.²⁴ They also recommend cystectomy as the next line of treatment in early BCG failures (in patients who can tolerate it) because of the increased risk of developing MIBC. National Comprehensive Cancer Network guidelines also recommend early cystectomy for patients with recurrence after BCG, although these guidelines do not clearly define BCG failure. Early cystectomy is widely recommended because it is superior in the oncologic control of BCG-refractory bladder cancer. However, in the patient who is not fit for cystectomy, refuses cystectomy, or has a late or low-grade recurrence after BCG, there are multiple agents for salvage therapy, which are examined in the remainder of this article.

SALVAGE AGENTS

Mitomycin C

Mitomycin C (MMC) is an alkylating agent that causes DNA cross-linking and inhibition of DNA synthesis (Table 1).²⁵ It is widely used in NMIBC as an adjunct to TUR in preventing tumor recurrence, and can be used postoperatively and with

Table 1
Generalized dosing schedules based on phase I-III trials

Agent	Mechanism of Action	Dose	Duration	Frequency	Maintenance	Notes	References
Mitomycin C	Alkylating agent, cross-links DNA, inhibits DNA synthesis	40 mg in 20 mL sterile water				Can administer immediately after TURBT × 1 Can cause chemical cystitis	
Thermochemotherapy	Local microwave hyperthermia by catheter improves drug penetration, causes local cytotoxicity	20–40 mg in 50 mL sterile water	Two consecutive 30-min instillations	Weekly × 6 wk	Monthly × 6 mo	Administer 20–40 d after TURBT	29–33
Electromotive Drug Administration	Electric current by catheter enhances membrane permeability	40 mg in 100 mL sterile water	30 min at 23–25 mA	Weekly × 6 wk	None	Must wash bladder before administration Start 3 wk after TURBT May also give preoperatively × 1	27,36–39
BCG-IFN	Stimulates immune response	BCG + 50 million units IFN- α in 50 mL sterile saline	1–2 h	Weekly × 6 wk	3 weekly instillations at 3, 6, 12, 18, 24 mo	If BCG-naïve, use full-strength BCG If BCG-refractory, use one-third strength BCG Dose reduction as needed	42–44
Gemcitabine	Nucleoside analog, inhibits DNA synthesis	2000 mg in 50–100 mL sterile saline	1–2 h	Weekly × 6 wk	Monthly × 10 mo	Maintain urine pH 5.5–7.0	50–54

Valrubicin	Semisynthetic anthracycline, inhibits nucleic acid synthesis and topoisomerase II	800 mg in 75 mL sterile saline	2 h	Weekly × 6 wk	None	Administer 2 wk after TURBT Food and Drug Administration approved for BCG refractory CIS	^{55–57}
Docetaxel	Microtubule stabilizer, inhibits mitosis and induces apoptosis	75 mg in 100 mL sterile saline	2 h	Weekly × 6 wk	Monthly × 9 mo	Administer 1–6 wk after TURBT	^{60,61}
Paclitaxel	Microtubule stabilizer, inhibits mitosis and induces apoptosis						
Nanoparticle albumin-bound	Nanoparticle albumin-bound formulation improves solubility and uptake by urothelium	500 mg in 100 mL sterile saline	2 h	Weekly × 6 wk	Monthly × 9 mo		⁶⁶
Hyaluronic Acid	Conjugation to HA improves solubility and uptake by urothelium	600 mg in 50 mL isotonic solution	2 h	Weekly × 6 wk	None		⁶⁹
Mycobacterial cell wall-DNA complex	Mycobacterial cell wall stimulates immune response without live vaccine	8 mg in 50 mL sterile saline	2 h	Weekly × 6 wk	3 weekly instillations at 3, 6, 12, 18, 24 mo	Administer within 60 d of TURBT	^{72,73}
Gemcitabine plus Mitomycin C	Combination therapy to maximize cytotoxic effects	1000 mg gemcitabine in 50 mL sterile water; 40 mg MMC in 20 mL sterile water	90 min for gemcitabine 90 min for MMC	Weekly × 6 wk	Monthly × 12 mo		⁷⁴

maintenance. However, it can cause significant chemical cystitis, and has not proved effective in the setting of BCG failure. A randomized prospective study of BCG versus MMC showed a recurrence-free rate of only 19% (4 of 21) in the group that crossed over to MMC (median follow-up, 64 months).²⁶ These low success rates have been attributed in part to inadequate drug delivery and tissue penetration, leading to assistive devices that use hyperthermia and electric current, allowing for more effective uptake of drug into the urothelial cells.^{27,28} Both modalities have been used in patients after BCG failure with improved results.

Thermochemotherapy

Thermochemotherapy (TCT) uses local microwave-hyperthermia to the bladder, by way of a specialized catheter, to a temperature of $42\text{C} \pm 2^\circ\text{C}$ (Synergo, Medical Enterprises, Amsterdam, the Netherlands).²⁹ The heat improves drug penetration into the urothelium, and is also cytotoxic, damaging DNA and inducing apoptosis.^{30–32} Nativ and colleagues³³ reported their retrospective view of 111 patients with prior BCG failure who had undergone TCT-MMC treatment with six weekly treatments of 20 mg MMC with two consecutive 30-minute cycles of TCT, followed by maintenance therapy as warranted. Recurrence-free rates were 85% (1 year) and 56% (2 years), and the average time to recurrence was 16 months. Patients were stratified by BCG failure categories (refractory, recurrent, resistant, intolerant),¹¹ and there was no significant difference in response rates. The 2-year recurrence rate for the BCG-refractory group was 56% versus 44% in the other groups. Completion of maintenance was the only factor found to correlate with lower recurrence rates. Forty-five percent of patients experienced adverse events, mostly local urinary toxicities, and 5.4% patients withdrew because of significant side effects. There is no comparison group in this retrospective review; however, a significant 2-year recurrence-free rate was seen in a high-risk group of patients.

Electromotive MMC

Another mechanism of enhancing intravesical drug efficacy is electromotive delivery.³⁴ Electromotive drug administration (EMDA) involves enhancing membrane permeability and drug transport by way of electric current. MMC is not ionic at urinary pH states, and thus requires a salt-containing solution to aid with transport across urothelial membranes.³⁵ Physionizer 30 (Physion, Mirandola, Italy) allows for a gradual increase in the current by a transurethral catheter, to a maximum of 23 to 25 mA, with a total

treatment time of 30 minutes. EMDA-MMC has shown superiority over MMC in a randomized trial of 108 patients with CIS (solitary or concurrent T1) with response rates of 58% (EMDA-MMC) and 31% (MMC) at 6 months, and median time to recurrence of 35 versus 19.5 months.²⁷ A third arm in this study received induction BCG with recurrence rates similar to that of EMDA-MMC. Long-term follow-up of 82 months showed similar equivalence of EMDA-MMC to BCG, and superiority to MMC alone with regards to recurrence, but no significant difference with overall survival or disease-specific survival.³⁶

The previously mentioned trial did not include BCG-failure patients, and so Sockett and colleagues³⁷ reported on 13 BCG-failure patients who received a 6-week course of EMDA-MMC, with a 31% recurrence-free rate at 15-month follow-up. EMDA-MMC has also been evaluated in conjunction with BCG in a randomized trial of 212 patients, and was shown to be more effective in reducing recurrence, progression, and all-cause and cancer-specific mortality than BCG alone.³⁸ Additionally, it has been shown to be safe and effective immediately before transurethral resection of bladder tumor (TURBT) in a BCG-naïve population.³⁹

MMC's activity in preventing tumor recurrence seems to be enhanced by TCT and EDMA technology, and is relatively well-tolerated. However, these tools have not been widely studied in the BCG-failure population, aside from Colombo and colleagues²⁸ prospective trial, nor have the two modalities been directly compared with each other. There are currently no known ongoing trials evaluating enhanced MMC after BCG failure, and these treatments will likely be targeted more toward incident NMIBC.

BCG and Interferon

Because BCG acts by eliciting an immune response, the immunostimulant interferon (IFN)- $\alpha 2b$ was introduced as another intravesical agent, showing some short-term efficacy alone.^{40,41} O'Donnell and colleagues⁴² published their experience in using BCG-IFN in patients with BCG failure, hypothesizing that patients failed because of an incomplete immune response, and that the addition of IFN would enhance the immunotherapeutic effect. Forty patients were given 6 to 8 weeks of induction BCG (one-third strength) and IFN, with further BCG dose reduction for patients with treatment intolerance. CR rates of 63% and 53% were seen at 12 and 24 months, respectively, and at 30-month median follow-up, 22 (55%) of 40 of patients were disease free. Initial induction treatments were well-tolerated, but treatment discontinuation was encountered with progressive

maintenance treatments, and 40% of patients ended therapy early because of intolerance.

Given these promising results, a multicenter phase II trial enrolled 1106 patients to receive BCG-IFN, inclusive of all types of NMIBC, regardless of prior treatment status.⁴³ BCG-naïve patients received full-strength BCG-IFN, whereas reduced strength BCG was given to BCG-recurrent or BCG-intolerant subjects, with maintenance given to responders as tolerated. Of the 467 BCG-failure patients enrolled, 39% had received at least two courses of prior BCG, and 47% had recurred or persisted at 6 months, indicating a BCG-refractory state, whereas the remaining 53% were BCG-relapsing. At 24 months, 45% of prior BCG-failure patients were disease-free, and on multivariate analysis, patients with at least two prior courses of BCG had a significantly worse outcome than those with none or one courses.

Rosevear and colleagues⁴⁴ re-examined the 231 subjects in the previously mentioned phase II trial who had CIS immediately before enrollment (63% CIS alone, 37% concurrent with Ta or T1), 52% of whom were BCG failures. Response rates at 24 months were 23% (failed ≥ 2 courses BCG); 57% (failed one course); and 60% (BCG-naïve). On multivariate analysis, having two or more courses of BCG was a significant risk factor for BCG-IFN failure, as compared with less than or equal to one course (hazard ratio, 2.003), as was BCG refractory disease, compared with intermediate BCG recurrence (>12 months) with a hazard ratio of 1.547. BCG-IFN seems to be an effective and safe salvage therapy, displaying acceptable response rates at 2 years. However, individuals who have failed multiple courses of BCG and those with early failure are less responsive to BCG-IFN combination therapy, and should consider early cystectomy if deemed appropriate.

Gemcitabine

Gemcitabine (Gemzar) is another antineoplastic agent used systemically in many cancers and has proved effective in combination with cisplatin (with or without paclitaxel) for treating metastatic urothelial cancer, and in the neoadjuvant setting before cystectomy.^{45–49} Gemcitabine is a nucleoside analog and is incorporated into DNA, halting DNA synthesis, thus leading to cell death.⁵⁰ It also irreversibly inhibits ribonucleotide reductase, preventing deoxyribonucleotide production, subsequent DNA synthesis, and repair, thereby inducing apoptosis.

A phase II trial by Dalbagni and colleagues⁵⁰ at Memorial Sloan Kettering Cancer Center evaluated 30 patients who had failed BCG and were refusing

cystectomy; 23 had CIS only. Gemcitabine was administered twice weekly for two 3-week periods with 1 week of rest in between, at a dose of 2000 mg (the highest soluble dose). At 3-month assessment, 50% (15 of 30) of patients achieved a CR, whereas 23% (7 of 30) had a partial response, defined as a negative cystoscopy and biopsy, but positive cytology. Of the 15 initial complete responders, 12 recurred at a median of 3.6 months, with one case of progression. Half of all nonresponders underwent cystectomy, whereas the other half ($N = 4$) had not shown disease progression at a median follow-up of 19 months. Ultimately, 10% of all patients were recurrence-free at 1 year. Eight grade 3 toxicities were reported, 75% of which were dysuria or frequency, one requiring cystectomy despite no evidence of disease.

This phase II trial enrolled a very high-risk population, with most patients being truly BCG-refractory after two prior induction cycles. A significant initial response rate was seen (50%); however, the response was not durable in most patients. Maintenance therapy was not evaluated in this trial, and many patients went on to cystectomy, making it difficult to determine the long-term rates of recurrence and progression.

Gacci and colleagues⁵¹ reported on a group of nine patients who had failed two BCG induction courses. This cohort received 6 weeks of intravesical gemcitabine, followed by a maintenance schedule of 3 weekly instillations at 3, 6, 12, 18, and 24 months. Again, it was well-tolerated, but six (67%) of nine patients recurred, anywhere from 4 to 19 months after onset of treatment. Two of those patients recurred with cT2 disease, and subsequently underwent cystectomy, and were alive without recurrence at last follow-up. Three patients remained recurrence-free at 13, 17, and 21 months of follow-up. Although this is a small pilot study, it confirms the tolerability of gemcitabine, and raises the possibility of using maintenance therapy for initial responders.

A larger multicenter phase II trial was conducted by Bartoletti and colleagues⁵² using intravesical gemcitabine, treating 116 patients with Ta, T1, or CIS, 40 (35%) of whom had failed BCG treatment, using the definition of persistent disease at 6 months postinduction. A total of 17.5% of patients reported adverse effects, requiring cessation of treatment in two cases. In the absence of maintenance therapy, at 1-year follow-up, 25.4% recurred at a median of 7 months. The subset analysis of the BCG failure group indicated that recurrence rates may be slightly higher, although it did not reach statistical significance. Overall, gemcitabine was more effective in patients with superficial disease and with no prior history of intravesical treatment.

In 2010, Addeo and colleagues⁵³ reported results of a randomized phase III trial, comparing intravesical gemcitabine with MMC for recurrent NMIBC. The gemcitabine treatment course consisted of a 6-week induction course, followed by 10 monthly maintenance treatments for initial responders. Of 120 enrolled patients, 109 were ultimately randomized with 54 and 55 patients in each treatment arm, respectively. A total of 91 patients had prior BCG treatment, although definitions of failure were not provided. At a median follow-up of 36 months, disease-free survival was superior in the gemcitabine arm, which was a consistent finding in the pretrial grade 3 histology group. Tumor progression occurred in 10 (18%) of 55 MMC patients, and in 6 (11%) of 54 of gemcitabine patients. With regards to adverse effects, MMC had a significantly higher rate (72.2% vs 38.8%), particularly with chemical cystitis (21.1% vs 5.5%) and dysuria frequency (20% vs 9.2%). Treatment delay occurred 10% of the time with MMC, and only 5% of the time for gemcitabine. In this phase III trial with many high-risk BCG-failure patients, gemcitabine proved slightly better at preventing recurrence, and had fewer adverse effects compared with MMC.

Recently, a national phase II nonrandomized study of monthly maintenance for intravesical gemcitabine (SWOG S0353) was completed.⁵⁴ Forty-seven patients who had failed two or more courses of BCG were treated, including patients with CIS (60%). At 3-month evaluation, 21 (45%) were disease-free, and 13 of those were continuously disease-free at the 12 months (28% of all evaluable patients). Three grade 3 toxicities were reported, whereas 30 patients had grade 1 to 2 toxicities, most of which were dysuria and urinary frequency. These data for gemcitabine maintenance therapy in a high-risk BCG-failure group indicate that a sizable portion of patients respond to therapy with a tolerable side effect profile, consistent with prior studies. However, it remains to be seen whether or not maintenance therapy adds benefit in preventing long-term progression and recurrence.

Although its efficacy has been illustrated in systemic disease, gemcitabine's role as an intravesical agent is still being evaluated. Phase I and II trials have shown it to be safe and somewhat effective in the treatment of recurrent NMIBC. The study populations have been somewhat heterogeneous, but have included many patients who have previously failed two induction courses of BCG and are thus at highest risk of recurrence and progression. Initial response rates of up to 50% have been reported and durable responses (disease free at ≥ 1 year) in 28% of patients, with the addition of maintenance therapy.

Valrubicin

Valrubicin (Valstar) is the only intravesical agent currently approved by the Food and Drug Administration for the treatment of BCG-refractory NMIBC. Valrubicin was developed as a lipid-soluble semi-synthetic analog of doxorubicin (adriamycin), with modifications allowing for more rapid uptake into cells, and less potential for cardiac toxicity.⁵⁵ It interferes with nucleoside incorporation into nucleic acids, causing chromosomal damage. It is also converted in the cytoplasm to *N*-trifluoroacetyl-adriamycin, which then binds to topoisomerase II, inhibiting DNA repair and replication, RNA and protein synthesis, and ultimately results in cell cycle arrest during the G2 phase.

Greenberg and colleagues⁵⁵ reported the first experience with intravesical valrubicin in 1997, in a trial of 32 patients, 22 (69%) of whom had CIS after BCG treatment. Most patients experienced adverse effects, mostly limited to grade 1 to 2 urinary toxicity. In short-term follow-up, a CR rate of 41% was seen. A phase I trial enrolling 22 patients evaluated the safety of immediate post-TUR administration of valrubicin.⁵⁶ This modality was found to be well-tolerated, with minimal systemic absorption, significant only in a patient who experienced bladder perforation. Response rates were not reported.

This led to a multi-institutional study reported by Steinberg and colleagues⁵⁷ enrolling 90 patients with CIS who had received at least one prior course of BCG. Six weekly doses of 800-mg valrubicin were administered intravesically, based on prior dose escalation studies. A CR rate of 21% (19 of 90) was observed, defined as no disease at 3- or 6-month follow-up. For these 19 patients, median time to failure or last evaluation was more than 18 months, with seven patients (8%) still disease-free at a mean of 30 months of follow-up. Forty-four patients had cystectomy, with median time to cystectomy of 24 months for the nonresponders. Six cystectomy patients had greater than or equal to pT3a disease, and two had pN+ disease. Four patients have died of bladder cancer, none of whom was a complete responder. Treatment was well-tolerated, with local urinary toxicity as the primary complaint. Based on these data, valrubicin was approved by the Food and Drug Administration for intravesical treatment of BCG-refractory bladder cancer in patients who cannot tolerate the morbidity and mortality associated with cystectomy.

Docetaxel

Taxanes are chemotherapeutic agents that stabilize microtubules, preventing cell division and

subsequently cause M-phase cell cycle arrest. They are used widely in oncology, and have shown efficacy in metastatic bladder cancer.^{58,59} Intravesical docetaxel (Taxotere) was first studied in a phase I trial in which 18 patients with NMIBC who had failed BCG or BCG-IFN received 6 weekly instillations.⁶⁰ Eight patients (44%) reported grade 1 to 2 toxicity, including hematuria, urgency, and dysuria, whereas none experienced grade 3 to 4 toxicity, and a maximum tolerated dose was not reached. All patients completed six treatments, and there was no drug detected on serum measurements. Results of the original cohort of patients have been recently reported with a median follow-up of 48 months.⁶¹ No delayed toxicity was reported, and 4 (22%) of 18 had a durable CR without maintenance or any other therapy, whereas 3 (17%) of 18 had a durable partial response, meaning a non-muscle invasive recurrence treated by local resection.

Paclitaxel

Because intravesical docetaxel was shown to be well-tolerated in patients with BCG-refractory NMIBC⁶⁰ another taxane was investigated in a phase I trial of *nab*-paclitaxel (Abraxane), a nanoparticle albumin-bound formulation that facilitates drug delivery into cells.^{62–65} The *nab* technology also allows for higher concentrations of taxane to be administered, which is important to note, because the maximum tolerated dose was never reached with docetaxel.⁶⁰ Eighteen patients with NMIBC were enrolled in this phase I dose escalation study in 2008 to 2009, all of whom had had at least one course of BCG induction, with a mean of 2.8 prior courses.⁶⁶ Twelve of the eighteen had also received BCG-IFN therapy, and three had received MMC, whereas three had received other experimental intravesical agents. No grade 2 or higher toxicities were noted, whereas 10 of 18 patients experienced grade 1 local toxicity, none of which required cessation of treatment. There was only one instance of detectable serum levels of paclitaxel, which resolved within a week. At first follow-up assessment, 5 (28%) of 18 patients demonstrated a CR. The efficacy of *nab*-paclitaxel is currently being evaluated in an ongoing phase II trial (clinicaltrials.gov ID NCT00583349).

An alternative drug delivery platform is hyaluronic acid (HA), a glycosaminoglycan abundant in human connective tissues. Binding HA to paclitaxel was shown to increase solubility and to increase in vitro antitumor activity, without systemic absorption in animal models.^{67,68} Bassi and colleagues⁶⁹ published a phase I study of

intravesical paclitaxel-HA (ONCOFID-P-B), enrolling 16 patients with BCG-refractory CIS, with 15 of 16 receiving all 6 weekly instillations. A total of seven patients reported 11 adverse events, three of which were serious, including exacerbation of pre-existing atrial fibrillation, resultant heart failure, and significant hematuria after a bladder biopsy 40 days after drug administration. At post-treatment assessment, 9 (60%) of 16 exhibited a CR. This phase I study indicates that a different formulation of paclitaxel may also be safe to administer intravesically in patients with BCG-refractory CIS; it is not clear if the significant adverse events were treatment-related. A phase II study using paclitaxel-HA for patients with G1-G2 Ta urothelial cancer is currently enrolling patients in Europe, but it excludes patients with CIS or T1 lesions, and does not require prior BCG failure, making it less applicable for patients seeking salvage therapy after BCG failure. It is hoped that it will shed more light on the overall efficacy of intravesical taxanes.

Mycobacterial Cell Wall Extract

BCG has been proved as the most effective agent in high-risk NMIBC, but carries the risk of BCG sepsis, because it is a live attenuated vaccine. To retain antitumor efficacy but reduce toxicity, the concept of using mycobacterial cell wall extract came about, and was first reported in 2001 as intravesical treatment in patients with CIS.^{70,71} However, the emulsion contained thimerosal, which has its own toxicities. Subsequently, a mycobacterial cell wall-DNA complex (MCC) was developed, and a multi-institutional open label study with 55 patients was conducted.⁷² MCC was administered weekly for 6 weeks, and then for 3 weeks at Weeks 12 and 24 as maintenance therapy. Twenty-eight patients in this cohort had had prior BCG therapy, whereas eight patients had no history of intravesical therapy. In the intention-to-treat analysis, response rates of 27% (4 mg) and 46% (8 mg) were seen at 12 weeks with identical rates at 26 weeks. At 18 months, disease-free rates of 23% (4 mg) and 29% (8 mg) were noted. Serious adverse events occurred at rates of 32% and 33% in the 4-mg and 8-mg of MCC groups, respectively, one of which necessitated treatment cessation.

Currently, a phase III trial is ongoing (clinicaltrials.gov ID: NCT00406068) using MCC in patients with BCG-refractory disease, or recurrent high-grade NMIBC less than or equal to 2 years after initial BCG success.⁷³ Eight milligrams of MCC was administered as a 6-week induction course, followed by 3 weekly instillations at 3, 6,

12, 18, and 24 months as maintenance. Interim results of 129 patients in this multi-institutional trial show a 1-year disease-free survival rate of 25%, with recurrence at a median of 177 days. Eighty-six percent of patients reported a treatment-related adverse event, mostly urinary. Two patients had to cease treatment based on adverse effects (asthenia, vomiting). These interim results show some efficacy of MCC in patients who have failed BCG, although not as effective as repeat BCG induction.¹⁴ Again, there is no standard control agent for this population against which to compare these agents, but MCC does seem to elicit a response in a select group of patients. MCC was recently being evaluated in a phase III open-label, randomized trial as compared with MMC for BCG-failure patients ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01200992) ID: NCT01200992). However, the trial was closed early because of poor accrual. Ultimately, MCC may be better suited as an alternative to BCG in primary treatment of NMIBC, provided it has similar efficacy and less toxicity.

COMBINATION THERAPY

Each salvage agent discussed has yielded clinical responses in certain patients, but none with any appreciable superiority at this point in time. In addition, it is not clear which patients will respond. BCG-refractory status and two or more prior courses of BCG have been associated with worse

outcomes in some studies,^{15,43,44} but not all of these individuals fail salvage therapy. A more recent strategy to address the relative lack of efficacy of single-agent intravesical salvage regimens has been the pursuit of multidrug combination intravesical therapy.

Breyer and colleagues⁷⁴ used a combination of MMC and gemcitabine in 10 patients with BCG-intolerant or BCG-refractory disease, defined as a positive biopsy after two induction courses. One gram of gemcitabine was given and retained for 90 minutes, drained from the bladder, followed by 40 mg of MMC. This continued for 6 weeks, with monthly maintenance given to responders. Six patients (60%) had a CR at 3 months, and are recurrence-free at a median of 14 months (4–34 months). No significant adverse events were reported.

In 2012, Chen and colleagues⁷⁵ provided a retrospective report of 114 patients with BCG-naïve NMIBC who received a cocktail of intravesical MMC-doxorubicin-cisplatin.

In a nonrandomized comparison with a group that received BCG, recurrence rates were similar between the two groups, with fewer adverse effects reported in the MMC-doxorubicin-cisplatin group. Although this did not include a BCG-failure group, it suggests that a multidrug regimen is a tolerable and feasible option for intravesical treatment. Well-designed prospective trials using multiagent therapy have yet to be conducted, but it seems

Table 2 Ongoing and pending clinical trials			
Drug	Trial Number	Phase	Description
rAd-IFN/Syn3 (Instiladrin)	NCT01687244	II	Interferon-α2b transfected into urothelial cells by adenovirus vector
RAD001 (Everolimus)	NCT01259063	I/II	Intravesical gemcitabine plus oral everolimus (mTOR inhibitor)
Dovitinib	NCT01732107	II	Oral dovitinib (tyrosine kinase inhibitor) for patients with FGFR3 overexpression or mutation
Sunitinib	NCT01118351	II	Oral sunitinib (tyrosine kinase inhibitor)
EN3348	NCT01200992	III	Mycobacterial cell wall-DNA complex vs mitomycin C
ALT-801	NCT01625260	I/II	Recombinant protein–interleukin-2 plus anti-p53-receptor
DTA-H19/PEI	NCT00595088	II	dsDNA plasmid, diphtheria toxin gene under H19 regulation (upregulated in tumor cells)
CG0070	Pending	II	Granulocyte-macrophage colony-stimulating factor transfected into urothelial cells by adenovirus vector
nab-rapamycin	Pending	I/II	Intravesical nanoparticle albumin-bound rapamycin (mTOR inhibitor)

logical that multiple agents would be more effective in the intravesical setting, as has been shown through the use of multidrug systemic chemotherapy, such as methotrexate-vinblastine-doxorubicin-cisplatin and gemcitabine-cisplatin.

FUTURE THERAPIES

Each salvage agent used is based on prior systemic chemotherapy experience (eg, gemcitabine, taxanes), or builds on knowledge of existing intravesical agents (eg, TCT-MMC, EMDA-MMC, MCC). Many current trials (**Table 2**) focus on targeted therapies, guided by knowledge of bladder cancer pathogenesis, and by technology advances in drug development. CG0070 and oportuzumab monatox are two such intravesical drugs whose phase I and II trial results have recently been published.^{76,77} CG0070 is an oncolytic adenovirus that preferentially replicates in cells with defective retinoblastoma (Rb) pathways (typically seen in bladder cancer), and also encodes human granulocyte-macrophage colony-stimulating factor, resulting in targeted cytotoxicity. Oportuzumab monatox uses recombinant fusion protein technology to combine anti-EpCAM antibody with *Pseudomonas* exotoxin A, enabling preferential binding to urothelial cancer cells, and inducing apoptosis. Additionally, mammalian target of rapamycin (mTOR) inhibitors and tyrosine kinase inhibitors are under investigation, because those pathways have been linked to urothelial cancer pathogenesis, and provide a clear target for treatment.

Another important avenue of future research is to continue to elucidate molecular markers that predict sensitivity and resistance to systemic chemotherapeutic agents^{78–80} and other intravesical agents.⁸¹ A better understanding of this may enable treatment choices to be tailored to individual risk profiles. Despite ongoing efforts, there is currently no superior alternative for BCG-failure patients. However, it is hoped that advances in understanding genomic alterations of urothelial cancer and in drug development technology will result in effective targeted therapies and individualized treatment as an effective method of addressing BCG failure.

SUMMARY

BCG has been established as the primary treatment of high-risk NMIBC. However, if patients do not respond or later recur, the most reliable treatment option is cystectomy. For those who are unwilling or unable to undergo this significant procedure, there is a multitude of alternative intravesical therapies. Each has been shown to have

some degree of efficacy and has provided durable CRs for certain patients. However, with the existing evidence, it is difficult to recommend one agent over another, or over cystectomy, because none has proved itself as reliably effective. Further work needs to be done to determine the risk profile of each BCG-failure patient, and to establish durable and successful treatments for this high-risk group.

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Determining the Role of Cystectomy for High-grade T1 Urothelial Carcinoma

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KEYWORDS

• Bladder cancer • T1 • High grade • T1G3 • BCG • Cystectomy • Treatment

KEY POINTS

- Pathologic upstaging from initial high-grade T1 to muscle-invasive disease ($\geq$ T2) from either repeat resection or cystectomy ranges from 25% to 50% depending on whether muscle was present at initial resection.
- Long-term studies show progression rates of up to 50% for high-grade T1 urothelial carcinoma of the bladder with up to 30% cancer-specific death.
- Although there has been significant effort in identifying factors associated with aggressive behavior, molecular markers are not in routine clinical use and need further validation.
- Presence of concomitant carcinoma in situ, tumor multifocality, hydronephrosis, tumor size (greater than 3 cm), stage T1b, and presence of residual T1 at repeat resection deem a patient high risk and immediate cystectomy should be strongly considered.
- The incidence of lymph node involvement in patients treated with radical cystectomy for HGT1 bladder cancer is 12% to 15%.
- Immediate radical cystectomy can provide a cancer-specific survival of greater than 80% in properly staged patients.

INTRODUCTION

High-grade T1 (HGT1) urothelial carcinoma of the bladder is a potentially lethal disease that requires meticulous attention. The HGT1 group represents about 20% of the patients who present with non-muscle invasive bladder cancer (NMIBC).¹ These tumors have a high propensity to recur and progress to muscle invasion with associated risk of metastasis and death. Long-term studies show progression rates as high as 50% with more than 30% of patients succumbing to the disease.² As opposed to noninvasive disease (Ta or carcinoma in situ [CIS]) or muscle-invasive disease ($\geq$ T2), treatment guidelines are not concrete and considerable variation exists in treatment modalities. Most studies have short-term follow-up, making it difficult to assess the true long-term efficacy of

proposed treatment regimens. There are no randomized trials comparing intravesical therapy with up-front cystectomy for HGT1 bladder cancer, making valid conclusions more difficult. The few long-term studies of intravesical therapy for initial diagnosis of HGT1 disease show a discouraging rate of progression and disease-specific mortality. Further confounding the issue is the often considerable heterogeneity in the HGT1 patient population, depending on the presence or absence of CIS, multifocality, tumor differentiation, tumor within a diverticulum, and, most importantly, whether there is muscle present in the resected specimen. Although there is a refined understanding of some of the molecular mechanisms and biology of high-grade bladder cancer, the currently available tools cannot adequately

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differentiate patients who are best suited for aggressive initial management (ie, cystectomy).

Transurethral resection (TUR) of the bladder tumor (TURBT) alone has long been recognized as inadequate treatment, with 40% to 50% of patients progressing to stage T2 or greater disease in just 3 years.³ The addition of intravesical bacillus Calmette-Guérin (BCG) immunotherapy following TURBT has been shown in randomized trials to significantly improve the 10-year tumor progression-free and disease-specific survival rates compared with TURBT alone.⁴ This combination now constitutes the current standard first-line therapy. Patients who fail induction BCG therapy and/or have recurrent disease shortly following treatment are at significant risk of progression to muscle-invasive disease and radical cystectomy should be seriously considered.⁵⁻⁷ Second-line treatments for bladder preservation are generally not very effective. Additional intravesical agents in patients who develop a recurrence following BCG therapy include BCG plus interferon, mitomycin C, gemcitabine, Doxorubicin, docetaxel, apaziquone, various combinations of these agents, and newer investigational therapies. The outcomes of trials investigating salvage intravesical therapies are generally poor and have short follow-up.⁸⁻¹⁰ Because effective second-line bladder-sparing therapy using intravesical agents is not well established, many experts consider the standard treatment in this setting to be radical cystectomy. This article reviews the clinical and pathologic features that characterize HGT1 disease, with special emphasis on the role of early radical cystectomy.

PATHOLOGY

Optimal management of bladder cancer relies heavily on information garnered from TUR of the tumor. Grade, stage, and depth of tumor invasion play a fundamental role in subsequent prognostication and treatment strategies. In addition, depth of tumor invasion within the lamina propria, associated CIS, lymphovascular invasion (LVI), and aberrant differentiation all have been shown to be important risk factors for progression of HGT1 disease. Interpretation of lamina propria invasion may be difficult in TUR specimens, especially when there is a high degree of cautery artifact. In a study of centralized pathologic review of 1400 patients treated in 5 European Organization for Research and Treatment of Cancer (EORTC) randomized phase III trials comparing various adjuvant treatments for NMIBC, the investigators found significant variation in grade and stage. More than half the tumors (53%) were downstaged to Ta, whereas 10% of the cases were upstaged to

muscle-invasive (T2) disease. There was agreement on the diagnosis of HGT1 disease in only 50% of the cases.¹¹ In addition, there is considerable understaging of the disease, particularly when there is no muscle included in the resected specimen. The goal of TUR is eradication of the tumor whenever possible with adequate sampling of the muscularis propria. Fluorescence cystoscopy (blue light) using hexaminolevulinate (HAL) has recently been shown to improve the detection and complete resection of NMIBCs.¹² Numerous studies have now documented up to 50% understaging when muscle is absent from the TURBT specimen.^{13,14} Even when muscle is present in the resected specimen, adequate staging cannot be presumed since studies have shown that, even in that setting, there is still a 10% to 15% chance of upstaging to muscle-invasive disease. These patients are destined to fail with conservative therapy because intravesical agents are ineffective in this setting. The presence of muscle in a resected specimen does not automatically imply that it was derived from the tumor base. Jancke and colleagues¹⁵ investigated the presence of residual tumor in what they called the 'marginal resection' following complete TURBT for Ta/T1 disease. A marginal resection of 7 mm was removed following macroscopic resection of all visible tumors. Of the 94 patients evaluated, 24 (26%) had residual tumor in the marginal resection, which had a significant impact on recurrence. Incomplete tumor resection not only leads to early recurrence but, more importantly, is probably the source for tumor progression and dissemination. Cystectomy series for clinical T1 disease also reflect similar understaging with 30% to 40% of patients being upstaged to muscle-invasive disease. In the series from Vanderbilt University including 78 patients, 31 patients (40%) were upstaged to T2 disease. Final pathologic stage had a significant impact on survival, with 98% of patients with pathologic stage T1 being disease free during follow-up compared with 65% with stage pT2 or greater disease ($P<.01$).¹³

SUBSTAGING

The existence of muscularis mucosae within the subepithelial connective tissue has been well described and used for prognostication.¹⁶ However, the degree of development of this layer is variable.¹⁷ The depth of tumor invasion into the lamina propria has been proved to be associated with outcome.¹⁸⁻²⁰ Angulo and colleagues²¹ examined a series of 170 patients with HGT1 disease and differentiated 98 of them (58%) into those with tumor invasion confined to the lamina

propria (pT1a) and those with tumor infiltrating into the submucosa (pT1b). Cox regression analysis of pT1 subcategory showed the depth of subepithelial connective tissue invasion to be an independent prognostic factor ($P < .05$). Five-year recurrence-free survival (RFS) was 86% for patients with stage pT1a tumors compared with 52% of those with pT1b tumors. Several other investigators have replicated similar results corroborating the feasibility of substaging of T1 tumors. Other researchers have studied this concept with further granularity. Orsola and colleagues¹⁶ reported on 97 patients with T1 disease substaged according to invasion superficial to (T1a), into (T1b), or beyond the muscularis mucosae (T1c). They were able to subclassify 87% of the cases and, although the recurrence rate was similar for all groups, progression rate for deep lamina propria invasion (T1b and T1c) was significantly higher than for T1a tumors (34% vs 8%, $P = .016$). Multivariate analysis revealed depth of invasion and CIS to be the independent prognostic factors, with a hazard ratio (HR) of 4.47 and 3.19, respectively. However, a recent study by van Rhijn and colleagues²² found no association between depth of invasion and progression or disease-specific survival. However, they did introduce a novel substaging system of pT1 bladder cancer differentiating tumors into T1 microinvasive (T1m) and T1 extensive (T1e) tumors. They then determined the invasion of the muscularis mucosae–vascular plexus into T1a/b/c categories according to invasion above, into, or beyond the muscularis mucosae. They found substage (T1m/T1e) to be significant for progression and disease-specific survival but not substage according to depth of invasion (T1a/b/c). More significantly they were able to classify all 134 cases into the new substaging system (T1m/T1e). Others have corroborated the significance of microinvasive versus extensive-invasive T1 to be prognostic for recurrence, progression, and survival in the largest series of initial pT1 tumors ($n = 209$) reported thus far.²³ In their study, depth of invasion into the lamina propria was also not significant. Not all patients had a restaging TURBT. The finding that extensive invasion of the lamina propria is highly prognostic can help identify patients better suited for upfront cystectomy.

OTHER PROGNOSTIC FACTORS

Numerous other factors have been studied in an attempt to further stratify patients into low versus high risk of progression. Although there is generally limited information obtained from a

TURBT specimen, various clinicopathologic features are present that can help differentiate patients into risk categories. LVI and tumor location have been correlated with outcomes in cystectomy performed for clinical or pathologic T1 disease.^{24,25} In one study, nontrigonal tumor location was one of the factors significantly associated with prolonged RFS.²⁶ In addition, the specimen can be submitted for molecular marker analysis, which may elucidate the underlying biologic behavior of the tumors. van Rhijn and colleagues²⁷ performed a head-to-head comparison of the EORTC risk scores with 4 molecular markers in HGT1 bladder cancers treated conservatively with BCG. Their subclassification into the new system of T1m (microinvasive) versus T1e (extensive-invasive) was found to be the most important clinical variable in predicting progression to muscle-invasive disease. The study included 129 patients from two universities, and T1 substaging was performed using the new system (T1m/T1e), as well as according to depth of invasion within the lamina propria (T1a/b/c). The molecular markers studied were fibroblast growth factor receptor 3 (FGFR3) gene mutation and Ki-67, P53, P27 expression, all of which have significant prognostic value in predicting bladder cancer outcomes. Factors significant for progression were female gender, substage (T1m/T1e), and presence of CIS. Molecular markers were significant for progression in a multivariable model; however, its value was only modest.²⁷ Acikalin and colleagues²⁸ studied the clinical significance of maspin and Ki-67 expression in TURBT specimens from 68 patients with newly diagnosed T1 bladder cancer. Maspin expression was an independent predictor of recurrence and progression, with negative maspin expression having a 4.3 times higher risk of progression compared with maspin-positive patients. However, Ki-67 expression had no correlation with recurrence, progression, or cancer-specific mortality. Other studies of molecular markers including p53, Ki-67, Cox-2, and NMP-22 and cell cycle analysis (S phase fraction) have identified an association with increased progression risk.^{29–34} Although considerable effort has gone into identifying factors associated with aggressive behavior, these markers are not in routine clinical use and need validation in large series to establish whether they offer any additional information compared with routine histopathologic evaluation.

RESTAGING TURBT

As previously mentioned, there is significant understaging in patients with HGT1 disease. If muscle is absent from the initial resection, repeat

resection to include muscularis propria at the base of the tumor resection is mandatory because there is more than 50% probability of finding muscle-invasive disease.^{14,35} Over the past decade or so, it has become clear that, in all patients with HGT1 disease, resection of the tumor base is important not only from a prognostic standpoint but also as a potential therapeutic strategy. Even when muscle is present in the specimen, repeat resection can uncover occult muscle-invasive disease in at least 10% of cases, which has a profound impact on decision making.^{36–38}

The advantages of the restaging have been well documented and include not only better stage and risk stratification but also eradication of residual noninvasive disease for improved therapeutic response to intravesical therapy. When patients have undergone restaging TURBT, the risk of upstaging following cystectomy theoretically should be very low. This was shown in at least 1 small study from Memorial Sloan Kettering on a cohort of 71 patients with HGT1 disease of whom 15 underwent immediate cystectomy. Although 12 patients had residual disease found at cystectomy, only 2 were upstaged to muscle-invasive disease.³⁹ Herr and colleagues,⁴⁰ from the same institution, also showed that the presence of residual T1 disease on repeat TUR is associated with a significantly increased risk of progression to muscle-invasive disease. Of the 92 patients with T1 disease at resection, 82% progressed to muscle-invasive disease at 5 years as opposed to 19% of patients with less than T1 disease (pT0, pTa, CIS). This finding is strong evidence in favor of immediate cystectomy for patients who have residual HGT1 disease on restaging TURBT. Patients should be counseled accordingly when considering conservative management. Young patients and those with life expectancy of more than 10 to 15 years should almost certainly be advised against having intravesical treatment because the risk of recurrence and progression remains well beyond 5 years. This risk is continuous in patients treated conservatively, in contrast with patients who have a cystectomy, for which relapse is rare beyond 3 years.

In addition to providing critical assessment of pathologic features of the tumor, restaging TUR also seems to improve the response to BCG therapy. Herr and colleagues⁴¹ compared 132 patients who underwent a single TUR before BCG therapy with 215 patients who had undergone restaging TUR. Notwithstanding the limitations of a nonrandomized comparison, 75 (57%) of the single TUR group had recurrent tumor at the first cystoscopy versus 62 (29%) of the restaging TUR group. More importantly, 45 (34%) in the

former group later progressed to higher stage disease, compared with 16 (7%), respectively ($P = .001$). One of the most convincing studies supporting restaging TURBT came from a randomized trial reported by Divrik and colleagues⁴² in 2010. In this trial, 210 newly diagnosed patients with HGT1 disease were randomized between a single TUR versus a restaging TUR 2 to 6 weeks following initial resection. With an adequate median follow-up of more than 5 years, recurrence (71% vs 40%), progression (24% vs 7%), and cystectomy rates (24% vs 13%) were significantly higher in the single TUR group. There were 11 deaths caused by bladder cancer in the single TUR group compared with only 5 in the second TUR group ($P = .04$). This study was criticized for methodological flaws (8% of patients who were upstaged by second TUR were excluded from the study after randomization, albeit accounted for in the cystectomy rates), with probable overestimation of the benefits of second TUR.⁴³ Nevertheless, there are ample data in this study to show the decreased recurrence and progression rates with a second TUR.

TREATMENT OPTIONS

Intravesical Therapy

Over the past 2 decades, a multitude of published studies established the effectiveness of adjuvant intravesical therapy for treatment of NMIBC. Both mitomycin C and doxorubicin were shown to reduce the risk recurrence and rate of progression, with mitomycin C possibly being more effective.⁴⁴ Over the years, BCG was shown to be superior to intravesical chemotherapy and became the treatment of choice for conservative management of high-grade disease. There are several studies reporting a wide range of recurrence and progression rates most likely because of the significant heterogeneity in the studied population including additional risk factors, use of second TUR, and use of maintenance therapy.^{45–54} In one of the early studies published more than 20 years ago on adjuvant BCG following TUR for HGT1 disease, Cookson and Sarosdy⁵⁵ reported 91% tumor-free rate with a median follow-up of nearly 5 years with a progression rate of only 7%. Several randomized trials clearly documented the improvement in long-term tumor progression-free and disease-specific survival rates compared with TURBT alone. However, it became clear early on that patients who fail to achieve a complete response after the initial course of BCG were at significant risk of progression and death.⁵⁶ Short-term follow-up does not adequately document the

continuous risk of recurrence and progression compared with cystectomy series in which most recurrences occur within 3 years.⁵⁷

Cookson and colleagues² reported the results of 15 years of follow-up of high-risk patients (CIS, T1) randomized to TUR alone or combined with intravesical BCG. Of the 86 patients enrolled, 44% had stage T1 tumors. Forty-six (53%) patients had progression and 31 (36%) eventually underwent cystectomy. The 10-year and 15-year disease-specific survival rates were 70% and 63%, respectively. At 15 years, 34% of patients overall were dead of bladder cancer, underscoring the high-risk nature of this group of patients. These results support the use of initial aggressive local therapy in patients with high-risk superficial bladder cancer. Numerous studies have published long-term results of using adjuvant BCG for HGT1 disease (Table 1).^{45–53,58–68} Only a few studies have reported results beyond 5 years.^{48,49,51,53,54}

Although adjuvant intravesical BCG therapy after TUR for HGT1 bladder cancer is evidently effective, the study by Shahin and colleagues⁵³ showed that it may only delay the time to recurrence and cystectomy, and that BCG does not affect cancer-specific survival (CSS) in the long term. However, this study did not include maintenance therapy. In addition, a meta-analysis validated the benefit of adjuvant BCG on progression. This study, involving 24 trials and 4863 patients (including patients with Ta disease and CIS), showed a relative risk reduction of 27% for progression in patients receiving adjuvant BCG. However, this benefit was only seen in patients who received maintenance BCG therapy and overall there was no difference in treatment effect for CSS.⁶⁹

Predictors of Progression

Some experts advocate an initial conservative approach to HGT1 disease, with deferred cystectomy on progression. The problem with this approach is that patients allowed to progress are inherently at a disadvantage, as shown by the death rates, despite cystectomy, which range from 16% to 34%.^{2,53,54} This uncertainty has led some to investigate predictors of progression. In a review including more than 1000 patients with HGT1 disease treated with adjuvant BCG, Herr and colleagues⁷⁰ reported progression rates ranging from 13% to 48% with a median follow-up of 5 years. This wide range suggests the concept of risk stratification in patients with HGT1 disease.

Alkhateeb and colleagues⁷¹ examined the prognostic significance of prior tumor resection in cases of HGT1 bladder cancer by comparing 95 primary with 96 nonprimary T1 tumors with similar clinicopathologic characteristics treated with BCG. The progression rate for the primary versus the nonprimary group was 24.2% versus 39.6%, respectively ([HR 2.07], $P = .03$). This difference remained significant on multivariate Cox regression analysis; however, there was no difference between the groups in regards to recurrence or disease-specific mortality. Kakiashvili and colleagues⁷² examined clinicopathologic features of 136 patients from two university centers to find predictors of recurrence and progression, and found CIS as the only independent predictor for recurrence in multivariate analysis ($P = .011$). The investigators found no independent predictors of progression in 30% of the patients, many of which occurred beyond 3 years, again highlighting the significant and unpredictable risk in this patient

Table 1
Select series reporting long-term results with BCG for HGT1 bladder cancer

Study	No. Patients	Median Follow-up (mo)	Recurrence (%)	Progression (%)	DOD (%)
Pansadoro et al, ⁴⁵ 1995	50	42	16	12	2
Baniel et al, ⁴⁶ 1998	78	56	28	8	0
Lebret et al, ⁴⁷ 1998	35	45	23	17	6
Hurle et al, ⁴⁸ 1999	51	85	37	18	14
Patard et al, ⁴⁹ 2001	50	65	52	22	14
Kulkarni and Gupta, ⁵⁰ 2002	69	45	46	12	6
Pansadoro et al, ⁵¹ 2002	81	76	33	15	6
Peyromaure et al, ⁵² 2003	57	56	42	23	12
Shahin et al, ⁵³ 2003	92	64	70	33	23
Margel et al, ⁵⁴ 2007	78	107	35	18	16

Abbreviation: DOD, dead of disease.

population.⁷² Orsola and colleagues⁷³ recently reported on risk factors for finding disease following BCG therapy in HGT1 disease. Tumor size and CIS were associated with finding positive disease at 3 months following initial TURBT and adjuvant BCG therapy. Other studies have corroborated the finding that the presence of CIS is associated with an increased risk of progression and death caused by disease.^{19,74} The EORTC has recognized associated CIS as the most significant factor associated with risk of recurrence and progression at 5 years after BCG therapy.⁷⁵ It is therefore imperative that pathologists report associated CIS as a separate finding in the presence of HGT1 disease so patients can be counseled appropriately regarding their risk profile.

In addition, patients who have tumor recurrence and are treated with a second course of BCG are at significant risk of progression and death. In a study of 214 patients with high-risk disease who recurred with a T1 tumor, there was a 71% cumulative incidence of progression to muscle-invasive disease in those treated with a second course of BCG, with nearly half of these patients dying of disease compared with 28% of those who underwent cystectomy (31% dead of disease).⁷⁶ Thus a HGT1 recurrence following adjuvant BCG therapy portends a poor prognosis and there is ample evidence that supports early cystectomy for this extremely high-risk patient population. Response rates to repeat BCG therapy for HGT1 disease is poor and delaying definitive therapy has a profound effect on the ultimate outcome.

Some other studies have documented a higher risk of progression with tumor morphology with solid tumors having more than twice the risk of progression and death from bladder cancer as papillary tumors. Other factors such as tumor size and aberrant histology,⁷⁷ in addition to the number of T1 lesions (multifocality), have been associated with higher progression rates.^{21,78} LVI is an important pathologic finding in cystectomy specimens and has also been shown to have prognostic significance in HGT1 lesions.^{78,79}

Chemoradiation

The data relating to radiation therapy (RT) in the treatment of HGT1 bladder cancer are limited. There are some data suggesting that concurrent chemotherapy with RT can be effective in high-grade urothelial carcinoma. Results from Erlangen, Germany, on 84 patients with HGT1 tumors using a trimodality bladder-sparing approach with concurrent chemotherapy and radiation showed a 10-year progression-free rate of 71% and a

10-year disease-specific survival rate of 71%.⁸⁰ More than 80% of the survivors had an intact bladder and 70% were 'delighted' or 'pleased' with their urinary function. In contrast with these promising results, a randomized trial comparing RT with conservative therapy (observation or intravesical therapy with mitomycin C [MMC] or BCG) for HGT1 disease showed no difference in progression-free survival or RFS (29% in the control vs 31% in the RT arm ($P = .65$)).⁸¹ There are few reports of the effectiveness of trimodality therapy as a second-line treatment of bladder preservation in patients with recurrent HGT1 disease following BCG therapy. The Radiation Therapy Oncology Group (RTOG) opened a clinical trial (RTOG 0926, Douglas Dahl, principal investigator) to explore the efficacy of chemoradiation in patients with HGT1 disease. To be eligible for this trial, all patients must undergo a restaging TURBT with muscularis propria present in the specimen and no evidence of muscle-invasive disease. The primary objective is avoiding cystectomy without compromising survival.

RADICAL CYSTECTOMY

Most cystectomy series for HGT1 tumors include patients with high-risk disease who have failed prior intravesical therapy. Because cystectomy generally represents the most aggressive and ultimate treatment of HGT1 disease, any comparison with more conservative treatment is hampered at the start by significant selection bias. Because of the substantial understaging of disease, it is important to scrutinize these series to distinguish those reporting on clinical versus pathologic T1 disease. Given the significant clinical understaging of HGT1 disease, series without restaging TURBT cannot be directly compared with those who were adequately staged. Nevertheless, the outcome from early cystectomy for HGT1 disease is generally excellent, with recurrence and disease-specific survival curves generally flattening after 2 to 3 years. In addition, the number of patients with clinical (c) T1 disease who harbor occult lymph node metastasis is important in series that include an extended pelvic lymph node dissection. In one study of 66 patients with cT1 disease, 27% of the cases were upstaged and 12% of those patients who had concomitant CIS had pathologic nodal involvement. Patients with cT1 tumors with CIS had a significantly worse CSS. Cancer-specific mortality for the cohort of patients with cT1 disease was 22% but those who had pathologic T1 disease had 10-year CSS of 92%.⁵ If cystectomy is performed when the tumor is still confined to the lamina propria, most patients are cured. If treatment is delayed

until muscle invasion is clinically evident, cure rates decrease significantly.

Early Versus Delayed Cystectomy

Timing of cystectomy is of paramount importance and affects pathologic stage and outcome. There is continued debate on whether patients presenting with high-risk features can be first treated with intravesical therapy or should undergo immediate cystectomy. Notwithstanding the limitations of nonrandomized comparisons, numerous studies have shown an unfavorable effect on outcome for patients who undergo delayed cystectomy. Herr and Sogani⁸² examined the long-term outcome of 307 patients with high-risk NMIBC initially treated with TURBT and BCG, of whom 29% ultimately underwent cystectomy during a 15-year to 20-year follow-up period. Of the 90 patients who underwent cystectomy, 49% survived. Only 18% of the patients survived when cystectomy was performed for muscle-invasive disease after 2 years of follow-up, compared with 41% when cystectomy was performed before 2 years. Multivariate analysis revealed improved survival in those who underwent earlier rather than delayed cystectomy for relapse.⁸²

Although there are no randomized trials comparing early cystectomy with conservative management with intravesical therapy, Denzinger and colleagues⁸³ compared the long-term outcome in patients with HGT1 disease treated with early versus deferred cystectomy for recurrent or progressive disease after initial conservative management. They compared patients who had at least 2 of the known risk factors for progression (multifocality, tumor size, and CIS) during initial TURBT. All the patients were offered up-front cystectomy and 51% opted for early cystectomy, with the other 49% undergoing deferred cystectomy for recurrence of progressive disease. Similar to all other studies, there was a 30% upstaging seen in the cystectomy specimen. The 10-year CSS was 78% in the early cystectomy cohort compared with 51% in the deferred cystectomy group ($P < .01$). The presence of CIS was correlated with a lower CSS in the deferred cystectomy group. The study had selection bias because the patients who underwent deferred cystectomy had failed conservative management and therefore presumably were at higher risk than those who underwent immediate cystectomy. Nevertheless, the patients in the 2 groups were well matched and had similar initial risk factors. Because there will probably never be a randomized trial comparing immediate cystectomy with intravesical therapy, this study provides more convincing evidence that patients

with HGT1 disease who have more aggressive treatment early in the course of the disease have improved outcomes.

Other investigators have published similar results. Hautmann and colleagues⁸⁴ reported on a series of 274 patients with cT1 disease, of whom 175 were treated with immediate cystectomy compared with 99 who underwent delayed cystectomy for recurrence following intravesical treatment. The patients who underwent immediate cystectomy did not have a restaging TUR. The reported CSS was 78% for the immediate cystectomy group compared with 65% in the deferred group. The survival disadvantage in the deferred group was calculated at 17%. However, in a large series of 523 patients from Memorial Sloan Kettering with HGT1 disease who had undergone restaging TUR, Dalbagni and colleagues⁸⁵ did not find any difference in survival between the immediate versus deferred cystectomy group. Of the 523 patients, 417 were deemed true HGT1, of whom 84 underwent immediate cystectomy. Of the 333 patients who were initially managed conservatively, 59 eventually undergoing cystectomy. The need for deferred cystectomy was higher in those who were found to have T1 disease on restaging TUR, again highlighting the high-risk nature of this group of patients and stratifying patients who would benefit most from early radical cystectomy. This series differs from the other series in that treatment approach was highly tailored and all patients underwent restaging TUR.

Results from Radical Cystectomy for HGT1 Disease

When counseling patients regarding treatment options, it is important to discuss long-term results from cystectomy performed for HGT1 disease. There are several series from high-volume centers reporting excellent outcomes for up-front radical cystectomy, for clinical T1 (**Table 2**),^{5,8,13,83,86–91} or pathologic T1 disease (**Table 3**).^{92–96} Gupta and colleagues⁸⁸ reported outcomes on 167 patients with HGT1 disease who underwent radical cystectomy at 3 academic centers in the United States. Median follow-up was short at just less than 3 years. Nevertheless, the CSS was 81.5%. However, 17.5% of patients had lymph node metastases, although there was 50% understaging with 27.5% having extravesical disease. The only factor predicting disease recurrence (HR = 2.13) and mortality (HR = 2.75) was concomitant presence of CIS before cystectomy. In a larger multicenter study of 1136 patients who underwent radical cystectomy for clinical HGT1 disease, half were upstaged to muscle-invasive disease, one-third had

Table 2
Outcomes of radical cystectomy for HGT1 urothelial carcinoma of the bladder

Immediate or Early Radical Cystectomy for Clinical HGT1 Tumor							
Study	N	Median Follow-up	Prior BCG Therapy (%)	Upstaging (%)	LN+ (%)	Recurrence (%)	DSS (%)
Amling et al, ⁸⁶ 1969–1990	166	120	—	—	7	—	76
Thalmann et al, ⁸⁷ 1980–99	29	47	0	41	14	21	69
Gupta et al, ⁸⁸ 1984–2003	167	34	44	50	18	29	82
Weisner et al, ⁸⁹ 1989–2002	188	—	—	34	16	—	—
Bianco et al, ⁵ 1990–2000	66	48	27	27	9	78	78
Lambert et al, ⁸ 1990–2005	104	—	44	40	—	48	93
Masood and Mufti, ⁹⁰ 1992–2002	30	57	30	27	—	—	88
Dutta et al, ¹³ 1995–99	78	—	37	40	12	—	78
Denzinger et al, ⁸³ 1995–2005	54	61	0	26	—	—	78
Fritsche et al, ⁹¹ 2010 (multicenter)	113	48	—	51	16	—	65

Abbreviations: DSS, disease-specific survival; LN+, lymph node positive.

non-organ-confined disease, and 16% had positive lymph nodes. With a median follow-up of 48 months, 36% died of metastatic bladder cancer.⁹¹ The investigators concluded that patients with high risk of progression may benefit from early cystectomy. However, substantial understaging and high incidence of extravesical disease argues for better clinical staging (through updated imaging, re-staging TUR) to identify patients who would be candidates for neoadjuvant chemotherapy to improve survival rates.

In an analysis from the Surveillance Epidemiology and End Results (SEER) database from 2004 to 2007, Canter and colleagues⁹⁷ stratified patients who underwent radical cystectomy within 1 year of diagnosis of HGT1 bladder cancer. Of the nearly 8500 patients who were registered in the database as having HGT1 disease, less than 5% underwent radical cystectomy. As expected, these patients were significantly younger. However, CSS was not different between patients who underwent cystectomy versus nonsurgical management up to 3 years from diagnosis, although patients who did not undergo cystectomy had a significantly higher

death rate from other causes. Only about one-third of the patients who progressed to muscle-invasive disease achieved a durable cure. However, interpretation of SEER-based studies on HGT1 disease are limited given the short-term follow-up, the lack of information on use of BCG therapy, and the information on patients who underwent delayed cystectomy beyond 1 year after initial diagnosis of HGT1 disease. The Canadian Bladder Cancer Network series involving 306 patients from 8 different Canadian centers with 3-year follow-up, revealed a 5-year and 10-year disease-specific survival of 77% and 67%, respectively, 29% of the patients were upstaged to extravesical disease, and 26% had positive lymph nodes.⁹⁸

At our institution, there has always been a selective, but aggressive, approach to management of patients with high-grade T1 disease. In the large cohort of patients who underwent radical cystectomy at University of Southern California with long-term follow-up, 34% of the patients with clinical T1 bladder cancer were pathologically understaged, with only half having organ-confined disease and 14% having lymph node metastasis.⁹³

Table 3
Results from large cystectomy cohorts reporting on pT1 disease

Study	N	Median Follow-up	LN+ (%)	RFS
Pagano et al, ⁹² 1979–1987	74	60	—	71
Stein et al, ⁹³ 1971–1997	208	120	7	80 (5 y)
Madersbacher et al, ⁹⁴ 1985–2000	77	45	3	76 (5 y)
Hautman et al, ⁹⁵ 1986–2009	127	38	4	71 (10 y)
Shariat et al, ⁹⁶ 1984–2003 (multiinstitutional)	114	39	—	89 (20 y)

As expected, those who were upstaged at cystectomy had significantly worse RFS than those who remained at T1 or less on final pathology at cystectomy.⁹⁹ These results, published in 2001, predated routine use of restaging TUR. Most published results of outcomes following cystectomy focus on clinical T1 disease and have a heterogeneous group of patients many of whom have extravesical and lymph node–positive (LN+) disease. Many of these series do not include restaging TUR and have significant clinical understaging, and therefore do not reflect the outcome of pathologic disease. In our updated cohort of more than 1600 patients undergoing radical cystectomy for urothelial carcinoma of the bladder, we found 222 patients with no prior history of muscle-invasive disease who underwent radical cystectomy for high-grade disease ($\leq$ cT1N0M0) and had pathologic T1 disease at cystectomy. Median follow-up of this cohort was 14.3 years, thereby allowing adequate analysis of the long-term outcome of

patients with pT1 disease. In this cohort, 24 patients (11%) had LVI and 13 patients (6%) had positive lymph nodes. RFS at 5 and 10 years was 81% and 74%, respectively. In the patients with LN+ disease, the RFS at 5 years was 46%. In a multivariable analysis including age, p53 status, grade, CIS, multifocality, gender, prior intravesical therapy, lymph node status, and LVI, lymph node status and LVI were the only factors significantly associated with RFS (LN+, $P = .0002$; LVI, $P = .0071$) (Fig. 1, Daneshmand, 2012, unpublished data).

Indications for Immediate Cystectomy in HGT1

After more than 20 years of retrospective studies, it is still not possible to reliably predict the outcome of patients who present with high-grade T1 disease. These patients do not have superficial disease and such a designation should be reserved for patients with Ta or CIS disease only. Patients with HGT1 disease have invasive disease

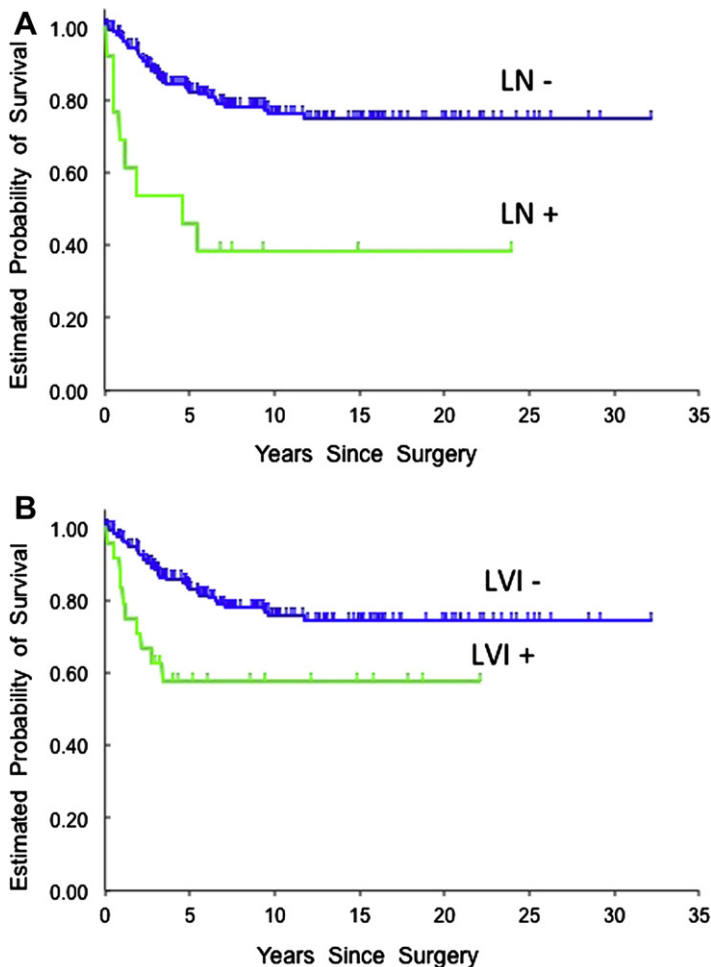


Fig. 1. Factors significantly associated with RFS in patients with pathologic T1 at cystectomy. LN–, lymph node negative.

that can progress to metastases and death. Owing to the vast difference in treatment strategy, there will probably never be a randomized study of radical cystectomy versus conservative treatment with cystectomy at progression. At this point, clinicians therefore have to rely on the wealth of retrospective data that can be used to guide optimal treatment strategies based on all available clinico-pathologic data. In a review article on treatment strategy for newly diagnosed HGT1 disease, Kulkarni and colleagues⁶⁸ presented a treatment algorithm for newly diagnosed HGT1 tumors and summarized the available data on risk factors for progression of the disease to use in recommending immediate or early cystectomy. Presence of concomitant CIS, tumor multifocality, hydronephrosis, tumor size (greater than 3 cm), stage T1b, and presence of residual T1 deem patients high risk. They suggested that patients with 2 or more risk factors of HGT1 disease at diagnosis should be advised to undergo immediate cystectomy. In cases of conservative management, presence of tumor at first surveillance cystoscopy following BCG, recurrent T1 disease, or prostatic urethral involvement during follow-up should trigger the decision to proceed with cystectomy. The international consensus panel has also recognized stratification of HGT1 tumors into low-risk and high-risk groups.¹⁰⁰ Others have also recommended management based on risk stratification including age and comorbidity status.¹⁰¹

The question remains whether patients with significant risk factors should still undergo restaging TUR to identify those at risk for extravesical disease or lymph node metastasis. Better approaches are necessary to identify the subset of patients with non-organ-confined disease who would benefit from neoadjuvant chemotherapy. The incidence of nodal involvement in patients treated with radical cystectomy for HGT1 bladder cancer is reportedly 12% to 15%.^{5,89,102,103} Clinical staging should be based on all available information, including bimanual examination in addition to cross-sectional imaging, not just TURBT stage, which may not give a clear picture of the aggressive nature of the disease. Patients who have clinical evidence of extravesical disease on imaging or have hydronephrosis are at higher risk of upstaging and should be considered for neoadjuvant chemotherapy before cystectomy.¹⁰⁴

In the era of restaging TUR, the indications for immediate cystectomy following initial TURBT for HGT1 tumors should be patients with 1 or more of the following:

- No evidence of extravesical disease on cross-sectional imaging performed at most

8 weeks before cystectomy, in whom restaging TUR will not change management

- Endoscopically unresectable disease
- Patient preference
- Poorly functioning bladder in a patient who will not tolerate intravesical therapy
- Multiple poor prognostic factors in a patient in whom restaging TUR will not change management (ie, potentially identify eligibility for neoadjuvant therapy)
- HGT1 tumor in a diverticulum, which precludes obtaining adequate muscularis propria

As previously mentioned, the pathologic stage at repeat TUR is a critical prognostic factor. In the cases upstaged to T2 disease, the decision is straightforward and these patients should proceed immediately to cystectomy. If restaging TUR reveals residual T1 disease, strong consideration should be given to cystectomy. The 5-year progression rate in this high-risk group of patients is 76% in the series reported by Herr and colleagues.¹⁰⁵ Patients who have no residual disease on restaging TUR have a better prognosis and can be managed conservatively with induction and maintenance BCG treatment.^{106,107}

The risks of both conservative (intravesical therapy) and aggressive (up-front radical cystectomy) treatment should be discussed with the patients. There is ample evidence that immediate cystectomy offers the best chance for cure, particularly in the presence of adverse features.⁷ There are several advantages for undergoing immediate or early radical cystectomy for HGT1 disease. It not only offers accurate pathologic staging but also identifies and potentially cures the subset of patients who have LN+ disease. Even with restaging TUR, a proportion of patients are still upstaged to muscle-invasive and/or LN+ disease.³⁹ Cystectomy also offers definitive treatment obviating multiple intravesical therapies, surveillance cystoscopies, and biopsies. The morbidity and inconvenience of repeated treatment and evaluation during conservative management should not be underestimated. In addition, as mentioned previously, the risk of progression with conservative management is continuous and lifelong, whereas most recurrences following cystectomy occur within 3 years.⁵⁷ Also, delaying cystectomy is associated with worse outcomes. The longer ineffective treatments are used for high-grade disease, the higher the risk of progression and metastases. Wiesner and colleagues⁸⁹ noted that the number of TURs performed for NMIBC (86% T1) was significantly associated with upstaging and lymph node metastases.

DISCUSSION

Radical cystectomy with thorough lymph node dissection provides accurate staging information, simplifies follow-up, and most patients are considered cured after 3 years. However, radical cystectomy is associated with significant morbidity, including effects on urinary continence, sexual function, and gastrointestinal function. Early cystectomy performed for HGT1 disease allows nerve-sparing approaches and most patients are candidates for orthotopic reconstruction, which has excellent results at high-volume centers.^{108,109} Reports of nerve-sparing cystectomy have shown good functional outcomes.^{110,111} In a series of 21 male patients undergoing nerve-sparing cystectomy, 79% were potent postoperatively, 58% with spontaneous complete tumescence.¹¹¹

The crux of the issue is balancing quality of life with effective cancer management. To that end, Kulkarni and colleagues¹¹² attempted to shed light on this dilemma by estimating quality-adjusted life expectancy (QALE). They used a decision analytical Markov model comparing immediate cystectomy with orthotopic neobladder with initial BCG with delayed cystectomy for refractory or progressive disease. For a sexually potent, 60-year-old, healthy male patient, the average life expectancy predicted by the model was almost 8 months longer with immediate cystectomy than with conservative management, whereas the QALE was 4.2 months longer with cystectomy. After age 70 years, the conservative treatment became the preferred approach. However, when considering QALE, this change in preferred treatment appeared at age 65 years. Additional comorbidities decreased the benefit of immediate cystectomy.

SUMMARY

HGT1 disease represents a heterogeneous group of tumors with variable clinical course. Current accepted treatment options include conservative management with induction and maintenance BCG therapy versus radical cystectomy with pelvic lymph node dissection. Clinical decisions should be made on risk of progression and patients with high-risk features including aberrant pathology, concomitant CIS, deep lamina propria invasion, LVI, involvement of prostatic urethra, large or multifocal tumors, and persistent HGT1 disease on re-staging TUR should be strongly considered for immediate cystectomy. Up to 70% of patients with HGT1 disease may be able to retain their bladders with appropriate conservative management. If cancer cure is the goal, immediate radical cystectomy can provide a CSS of greater than 90% in

properly staged patients. Those who are initially treated with conservative management but have high-grade disease recurrence at 3-month follow-up should also be advised to undergo cystectomy. Delay in definitive treatment with cystectomy in the high-risk patient is associated with significantly increased risk of progression and death caused by disease. Patients undergoing conservative treatment of HGT1 disease should undergo a 6-week course of induction BCG followed by maintenance BCG for the following 1 to 3 years with vigilant lifelong surveillance. At this point, investigational molecular markers have not substantially improved prognostication and their use needs further validation. Even radical cystectomy for pathologic T1 disease does not guarantee cure, indicating that a subset of HGT1 tumors have aggressive biologic behavior that requires identification and adjuvant therapy.

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The Conundrum of Prostatic Urethral Involvement

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KEYWORDS

• Non-muscle invasive bladder cancer • Prostatic urethra • Stromal involvement • Urothelial cancer

KEY POINTS

- The presence and depth of urothelial cancer involvement in the prostatic urethra can significantly affect the management of a patient with non-muscle invasive bladder cancer.
- Bladder tumor multifocality, carcinoma in situ, and tumor of the trigone and bladder neck have been associated with prostatic involvement.
- Transurethral resection loop biopsy of the precollicular area between 5 and 7 o'clock will identify most prostatic urethral involvement.
- Superficial and subendothelial tumors can be treated with bacillus Calmette-Guérin (BCG) instillation and close follow-up, and ductal involvement with BCG or cystoprostatectomy; however, stromal involvement warrants cystoprostatectomy.

INTRODUCTION

Urothelial carcinoma is a multifocal disease of the urothelium that can develop anywhere in the urinary tract, including the prostatic urethra. The lining of the prostatic urethra and the prostatic ducts have the same transitional cell urothelium as the bladder; therefore, it is not surprising that a patient who develops non-muscle invasive bladder cancer (NMIBC) can develop urothelial carcinoma in the prostatic urethra or ducts, either as an extension from the primary process or as a de novo entity.

Knowledge of urothelial cancer of the prostate is pertinent to the management on NMIBC for 3 reasons: the presence and depth of prostate urothelial cancer will affect prognosis¹; its presence in the prostatic urethra may suggest understaging of the primary tumor in the bladder²; and NMIBC managed conservatively can recur in the prostatic urethra.³

This article offers an overview of urothelial cancer in the setting of NMIBC, and its incidence, diagnosis, and management.

DEFINITIONS, CLASSIFICATIONS, AND STAGING

The prostate contains glands that consist of ducts and terminal acini that are in continuity with the transitional urothelium of the prostatic urethra and bladder. The ducts and acini are surrounded by the stroma, consisting of connective tissues and smooth muscle cells. The urothelium and the stroma are separated only by a thin basement membrane. The differences in anatomic and functional structure of the prostate, as well as the absence of muscularis propria, alter the natural history, staging, and management of urothelial cancer that occurs in this area. Involvement of prostatic urethra, ducts, acini, and stroma have all been described in patients with non-muscle invasive bladder transitional cell carcinoma.^{1,4,5} These entities each have distinctly different clinical significance and prognosis.¹

Conceptually urothelial cancer of the prostatic urethra can be confusing, so it is important to

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establish classifications and definitions before further discussion on diagnosis and management. A significant contributor to this problem is the different anatomic structure of the prostate and the fact that prostatic urothelial cancer can arise primarily in the prostate or as a direct extension of a primary bladder tumor.

As a result, prostatic urothelial cancer is included in two separate staging systems: first, a staging system for primary urothelial cancer arising in the prostate, and second, a staging system for primary urothelial cancer of the bladder that extends into the prostate. Table 1 illustrates the similarities and differences between the staging systems for these 2 anatomic sites.

It should be noted that the American Joint Cancer Committee staging system was only changed in 2010 to reflect these differences. Before the 2010 revision, any involvement of the prostate in a patient with bladder cancer was classified as stage T4a bladder cancer, regardless of depth of invasion.⁶ This classification was justly criticized, as convincing survival data suggest that primary prostatic urothelial cancer, as opposed to bladder cancer directly invading the prostate, carries a different prognosis, as does

involvement of the prostatic urethra with urothelial cancer of different depths of invasion.^{1,7–12} Examining the first question, Pagano and colleagues¹⁰ compared survival in patients with contiguous spread of bladder cancer to the prostate with those with a noncontiguous urothelial cancer arising within the prostate. Only 7% of the patients with a contiguous tumor were alive at 5 years compared with 46% of patients with a noncontiguous tumor. Examining the second question of prostatic stromal involvement in comparison with lesser degrees of tumor invasion, Esrig and colleagues⁷ investigated 143 men who underwent cystectomy and were found to have prostatic involvement; 5-year overall survival rates with and without stromal invasion were 36% and 71%, respectively. In addition, men without stromal invasion had a prognosis no worse than men without any prostatic involvement at all. Similarly, Solsona and colleagues⁸ found patients with prostatic stromal involvement to have a hazard ratio of 2.89 for cancer-specific mortality in comparison with those without stromal involvement. Herr and Donat³ investigated patients with NMIBC who had been treated with intravesical bacillus Calmette-Guérin (BCG) and had late recurrences

Table 1 American Joint Cancer Committee staging system, seventh (2010) version	
Urothelial Cancer of the Bladder	Urothelial Cancer of the Prostate
TX: Primary tumor cannot be assessed	
T0: No evidence of a primary tumor	
Ta: Noninvasive papillary carcinoma	
Tis: Noninvasive flat carcinoma (flat carcinoma in situ, or carcinoma in situ)	Tis pu: Carcinoma in situ, involvement of prostatic urethra Tis pd: Carcinoma in situ, involvement of prostatic ducts
T1: Tumor invades subepithelial connective tissue	T1: Tumor invades urethral subepithelial connective tissue
T2: The tumor invades muscularis propria T2a: Tumor invades the inner half of muscularis propria T2b: Tumor invades the outer half of muscularis propria	
T3: Tumor invades perivesicle tissue T3a: Microscopically T3b: Macroscopically	
T4: Tumor invades any of the following: prostatic stroma, seminal vesicles uterus, vagina, pelvic wall, abdominal wall T4a: Tumor invades prostatic stroma, uterus, vagina T4b: Tumor invades pelvic wall or abdominal wall	T2: Tumor invades prostatic stroma, corpus spongiosum, periurethral muscle T3: Tumor invades beyond prostatic capsule, corpus cavernosum, bladder neck T4: Tumor invades adjacent organs

Data from Edge SB, Byrd DR, Compton CC, et al, editors. AJCC cancer staging manual. 7th edition. New York: Springer; 2010.

in the prostate. Prognosis was highly dependent on depth of invasion, whereby survival rate was 82% in patients with prostatic urethral or ductal involvement, compared with 48% with those with stromal involvement.³ Examining the question of lesser degrees of prostatic involvement, Barocas and colleagues¹ investigated 3-year overall survival among 162 cystoprostatectomy patients with prostatic involvement. Three-year survival was 59% if the prostatic urethral involvement was carcinoma in situ (Tis pu), 52% if there was ductal involvement, and only 17% if there was stromal involvement.

INCIDENCE

When discussing the incidence of urothelial cancer involving the prostate it should be realized that isolated primary prostatic urothelial cancer is rare; instead this tumor is almost always associated with the presence of, or history of, urothelial cancer of the bladder.¹³ There is a moderate amount of data available on the incidence of urothelial cancer arising within the prostate in patients with bladder cancer, with reported overall incidence rates of 6% to 48%, with a 7% to 17% incidence of prostatic stromal involvement.¹⁴ Most of these data come from the cystoprostatectomy literature, which is heavily focused on muscle invasive bladder cancer and only includes NMIBC that has failed more conservative therapy. Therefore, much of the information is not directly applicable to the patient with newly diagnosed NMIBC.

The incidence figures for NMIBC-associated prostatic involvement also vary depending on the method by which the prostatic urethra is assessed (visual inspection, cold-cup biopsy, resectoscope biopsy, or pathologic analysis of the cystoprostatectomy specimen) and the timing and indications for the sample collection (diagnosis, investigation of isolated positive cytology, following intravesical therapy, or at the time of cystectomy).

In regard of the different sampling methodologies, the incidence of prostatic involvement reported following cold-cup biopsy is 24% to 27%. In these series Tis constitutes 69% to 100% of prostate pathology, and only 1 case of stromal invasion has been found.^{15,16} However, with cold-cup biopsy there is clearly a high frequency of inadequate sampling of the ducts and stroma. Most studies use a resectoscope to sample the prostate. Studies using a resectoscope loop biopsy have found a 6% to 36% rate of prostatic involvement with urothelial cancer.^{4,5,17,18} Many of these studies were designed to monitor outcomes of intravesical therapy whereby stromal

and sometimes ductal involvement were exclusion criteria; therefore, establishing the true incidence of ductal involvement can be difficult. In a series of 49 patients undergoing transurethral resection (TUR) for a bladder tumor and with biopsy of their prostatic urethra, Schellhammer and colleagues⁵ reported that 18 (37%) had prostatic involvement. Of these patients, 13 had identifiable ducts in the specimen and 7 of 13 (56%) harbored ductal urothelial cancer. Cystectomy data, although heavily focused on muscle invasive bladder cancer, have been reported in a few series that allow for subanalysis of NMIBC. In a cystectomy series of 192 patients, Nixon and colleagues¹⁹ found 42 men with Tis, or T1, bladder disease, 8 (19%) of whom had prostatic involvement. Similarly, in series by Liedberg and colleagues²⁰ and Mazzucchelli and colleagues,²¹ 5 of 19 men (26%) and 26 of 70 men (37%), respectively, with NMIBC were found to have prostatic involvement. Although these studies reported the overall rates of prostatic stromal involvement, this was not specified for the subset with NMIBC.

To sum up, the incidence rates of prostatic urethral involvement at initial diagnosis range from 6% to 37% and are dependent on sampling method and patient risk. The frequency of recurrence of urothelial cancer in the prostate following therapy for NMIBC ranges from 8% to 48%, and is explored in more detail in the next section.^{3,19,22-25}

RISK FACTORS FOR PROSTATIC URETHRAL INVOLVEMENT

If diagnosed, prostatic involvement may drastically affect both prognosis¹ and management of NMIBC. However, in most cases identification and diagnosis requires transurethral biopsy or resection of the prostatic urethra. As tissue biopsy of the prostate is not without potential morbidity, a moderate amount of work has gone into trying to identify which patients might benefit from sampling of the prostate. Numerous factors have been evaluated.

Much information can be gained from the cystectomy literature. Nixon and colleagues¹⁹ looked at 192 prostatectomy samples, of which 30 (15%) had prostatic urethral involvement. Patients with tumor multifocality and bladder carcinoma in situ (CIS) had rates of prostatic involvement of 34% and 31%, respectively. In a study by Mazzucchelli and colleagues,²¹ 94 out of 248 (38%) cystoprostatectomy specimens had prostatic urethral involvement. Trigonal or bladder neck tumor location, pT and pN stage, and previous history of recurrence were significant risk factors. Based on their data, a formula was constructed that

uses number of tumor foci in bladder, history of prior recurrence, and location of bladder tumor, which was able to predict with 61% sensitivity and 78% specificity whether there was a concomitant prostatic involvement. Other series have found numerous other factors associated with prostatic urethral involvement, including multifocal CIS, trigonal CIS, periurethral tissue invasion, ureter invasion, vascular invasion, history of bladder tumor recurrence, and history of prior bladder intillations.^{1,20,22,26,27}

In the transurethral literature it has been reported that macroscopic tumor in the urethra correctly identifies prostatic urethral involvement with a sensitivity of 83% and a specificity of 95%.¹⁹ However, Mungan and colleagues⁴ reported a series with an overall prostatic urethral involvement rate of 6.2% whereby macroscopic involvement was seen in 3.5% of cases. In the other 2.7% the urethra appeared normal. The same study found that on univariate analysis, stage, grade, and multifocality of the bladder tumors correlated with prostatic involvement, not macroscopic appearance of the prostatic urethra. On multivariate analysis, only bladder tumor multifocality significantly correlated with prostatic involvement. In this study the risk of developing prostatic involvement in the presence of multiple bladder tumors was 16 times higher than the risk conferred by stage or grade.

Cystoscopic inspection, therefore, has a high specificity in correctly identifying a macroscopic tumor but a low sensitivity in correctly identifying the presence of tumor when the urethra appears normal, especially in a high-risk patient. The risk factors that correlate best with the presence of prostatic urethral carcinoma include the presence of multifocal bladder tumors, CIS, and tumors located on the trigone or bladder neck.

The European Association of Urology (EAU) 2011 guidelines on NMIBC recommend biopsy of the prostatic urethra for cases of bladder-neck tumor, when bladder CIS is present or suspected, when there is positive cytology without evidence of tumor in the bladder, or when abnormalities of the prostatic urethra are visible.²⁸ The National Comprehensive Care Network (NCCN) recommends considering a TUR biopsy of the prostatic urethra if the bladder tumor is sessile, or there is suspicion of high-grade bladder tumor or bladder CIS.²⁹

Finally, whereas bladder tumor parameters can predict the presence of a prostatic urethral cancer, at least one study has investigated the converse, that is, the presence of prostatic urethral involvement as a risk factor for understaging of the primary bladder tumor. Huguet and colleagues²

evaluated 62 patients with Tis, T1, or Ta bladder cancer that had failed TUR and BCG and eventually went onto cystoprostatectomy. In their series, initial prostatic involvement was the only significant risk factor of upstaging of the bladder tumor to muscle or stromal invasive disease, with a hazard ratio of 12.2 (95% confidence interval 2.2–65.5).

DIAGNOSTIC METHOD

There are numerous reports of the different methods used to diagnose prostatic urothelial cancer. Most describe cold-cut biopsy or TUR, although fine-needle aspiration and transrectal ultrasound-guided biopsy have been used.²²

As mentioned in the previous section, the finding of a cystoscopically visible papillary lesion in the prostatic urethra on initial inspection has a high sensitivity and specificity for the presence of urothelial cancer.¹⁹ However, one should be cautious in patients with a prior history of intravesical BCG treatment. A study by Orihuela and colleagues²³ reported that 48% of biopsies of suspicious lesions were negative. The patient with a normal-appearing urethra, in the absence of risk factors (multiple bladder tumors, CIS, tumor at the bladder neck, and so forth), has a relatively low absolute risk of the presence of tumor (~6%); however, approximately 43% of prostatic urethral tumors are not visually apparent.⁴

Several studies have examined the sensitivity and specificity as well as the most appropriate technique with which to perform a prostatic urethral biopsy with the resectoscope loop. Donat and colleagues³⁰ performed a prospective TUR loop biopsy on 246 male patients who subsequently underwent cystoprostatectomy, and found the sensitivity and specificity for Tis to be 53% and 77%, for T1 57% and 89%, and for stromal invasion 56% and 93%. Liedberg and colleagues²⁰ reported a similar 66% sensitivity and 89% specificity for any prostatic urothelial cancer in their 175-patient cystoprostatectomy series.

Various investigators have studied how extensively and where the prostatic urethra ought to be sampled. Hillyard and colleagues¹⁷ initially described cold-cup biopsies and TUR biopsies of the lateral lobes. Taylor and colleagues,³¹ in a long-term follow-up of the same series, described additionally taking TUR resections proximal to the verumontanum. Liedberg and colleagues²⁰ described transurethral loop biopsies from the bladder neck to the verumontanum, obtained at the 4- and 8-o'clock positions. This approach is supported by Sakamoto and

colleagues³² who, based on pathologic evaluation of cystoprostatectomy specimens, found that firstly, 93% of urothelial cancer involving the prostatic urethra is superficial enough to be identified with a superficial resection and secondly, that 84% are located at the 5- and 7-o'clock positions. In their series, only 1 patient had deep stromal involvement without a superficial tumor being identified. Given that most of the tumors are detected superficially in the prostate, a complete TUR of the prostate is not indicated. Parenthetically, should a TUR of the prostate be indicated for lower urinary tract symptoms at the time of a bladder tumor resection, a recent meta-analysis suggests that this is quiet safe, with a low risk of tumor implantation in the prostate resection bed.³³

Accordingly, the technique most used to sample the prostatic urethra is a TUR at the 5- and 7-o'clock positions just proximal to the verumontanum, as this allows the surgeon to obtain a specimen of adequate depth and size to allow for pathologic assessment of mucosa, ducts, and stroma. This procedure is in agreement with the 2011 EAU guideline, which suggests that the biopsy should be taken "from abnormal areas and from the precollicular area (between 5 and 7 o'clock position) using a resection loop."²⁸

MANAGEMENT

The management of NMIBC with prostatic urethral involvement falls into 3 categories: Group 1, noninvasive papillary tumors and CIS of the prostatic urethra (pTa/T1 and pTis pu); Group 2, CIS involving the prostatic ducts (pTIS pd); and Group 3, prostatic stromal involvement (pT2–pT4). This section also discusses management of the urethra in patients undergoing cystectomy who have known preoperative prostatic urethral involvement.

Group 1: Noninvasive Papillary Tumors and CIS of the Prostatic Urethra (pTa/T1 and pTis pu)

There is mounting evidence that Tis pu and T1 can be managed with TUR and/or intravesical instillation. In the study by Donat and colleagues³⁰ discussed previously, a TUR (biopsy) was performed on 246 men with bladder cancers who subsequently underwent a cystoprostatectomy. Of those diagnosed with prostatic urothelial cancer by TUR, 45% had no urothelial cancer identified on whole-mount examination of the prostate. These findings suggest that TUR alone will be curative in a proportion of patients.

Chemotherapeutic agents such as mitomycin C, adriamycin, epirubicin, and BCG have been used for intravesical therapy in the conservative management of superficial tumors involving the prostatic urethra. Of these BCG has been most extensively investigated, and multiple small case series have reported complete response rates in the range of 48% to 87%.^{5,17,18,23,24} Intravesical chemotherapy has been reported to be somewhat less effective than BCG, with a complete response rate of 37% in a study by Solsona and colleagues²⁵ that used mitomycin C or adriamycin. In another small retrospective review of 19 patients, epirubicin was noted to have a response rate of 29% compared with 58% for BCG.³⁴

As the intravesical agents only make contact with the prostatic urothelium briefly during instillation and voiding, there is controversy as to the extent of penetration of intravesical therapy into the prostate. LaFontaine and colleagues³⁵ examined cystoprostatectomy specimens, and found that 75% of men with prior history of BCG bladder instillations had developed granulomatous prostatitis compared with 11% of men without prior BCG treatment. A similar finding by Oates and colleagues³⁶ of granulomatous response in 100% of prostates biopsied after BCG treatment supports the notion that BCG penetrates deeply. However, as a caveat, granulomatous inflammation can be seen in the prostate of patients who have not undergone BCG therapy, and a transurethral biopsy of the prostate has itself been shown to cause granulomatous prostatitis on occasion.²³

Some investigators have argued for TUR resections before BCG therapy to allow better penetration of the instillation into the prostate.¹⁷ Although BCG without TUR has been reported with a 78% initial complete response rate,¹⁸ most reported series use TUR with BCG. The outcomes of reported series evaluating BCG are shown in **Table 2**. **Table 2a** shows studies on Tis pu and Ta only while **Table 2c** shows data that include Tis pd, as these series are larger and with long follow-up.

EAU and NCCN guidelines, and a World Health Organization/Société Internationale d'Urologie (WHO/SIU) consensus, all state that Tis pu and T1 can be treated with BCG and that TUR can increase BCG contact with the prostate.^{28,29,37,38}

Limited data exist on how to manage prostatic recurrence of urothelial cancer after BCG treatment, as most series are reporting fewer than 5 recurrences.²³ TUR, another course of BCG, and cystoprostatectomy have all been described. Both NCCN and WHO/SIU recommend cystoprostatectomy for recurrent disease.^{29,38}

Table 2**Summary of the results of studies examining the efficacy of bacillus Calmette-Guérin (BCG) in patients with prostatic involvement**

Authors, ^{Ref.} Year	Complete Response (%)	Late Recurrence (%)	Progression	Transitioned to Cystectomy	Transitioned to Systemic Chemotherapy or Irradiation	Mean Follow-Up (mo)	Comment
(a) Ta and Tis pu Disease							
Orihuela et al, ²³ 1989	13/15 (87)	1/13 (8)	1/15	1/15 ^a		?	Tis pu + Ta Recurrence responded to TUR
Ovesen et al, ¹⁶ 1993	10/10 (100)	2/10 (20)				26	Tis pu
Palou et al, ¹⁸ 1996	14/18 (78)	5/14 (36)	3/18	3/18		31	Tis pu
Canda et al, ³⁴ 2004	7/12 (58)	2/12 (17)	3/12	1/12 ^a	4/12 ^a	64	Tis pu + Ta Recurrence responded to second round of BCG
(b) Tis pd Disease							
Palou Redorta et al, ³⁹ 2006	5/10 (50)	1/5	2/10	2/10	1/10		Tis pd
(c) Ta, Tis pu, and Tis pd Disease							
Bretton et al, ²⁴ 1989	13/23 (56)		10/23	8/10	2/10	42	Tis pu + Tis pd + Ta
Taylor et al, ³¹ 2007	18/28 (64)	10/18	15/28	8/28		89	Tis pu + Tis pd + Ta

^a These patients were nonresponders to intravesical BCG therapy.

Group 2: CIS Involving the Prostatic Ducts (pTis pd)

Treatment when there is acinar or ductal involvement is more controversial. There are essentially two options, TUR followed by BCG with surveillance cystoscopies or immediate cystoprostatectomy. The argument for BCG is the potential to avoid cystoprostatectomy and the associated morbidities with the need for urinary diversion. Most studies have very few patients, and head-to-head comparison has not been attempted. Studies from Bretton and colleagues²⁴ and Taylor and colleagues³¹ used TUR and BCG for patients with prostatic urethral involvement. Their data included Tis du disease.⁵ These studies showed reasonable complete response rates (see **Table 2c**), but long-term outcomes for patients with ductal involvement are not specifically stated. Palou Redorta and colleagues³⁹ report a BCG treatment series wherein all the patients had Tis pd (see **Table 2b**). Half of the 10 patients responded to therapy and 1 of 5 responders developed recurrence, thus only 40% were free of disease.

Some studies among patients who have undergone cystoprostatectomy show little or no difference in survival between patients with urethral tumors (Tis pu/Ta) and Tis pd patients.^{1,40} However, Wishnow and Ro⁴¹ report a series wherein 11% of patients with ductal disease went on to develop metastasis (although this number is small compared with the 100% of patients with stromal involvement). These investigators argue that because there is only a thin layer of connective tissue preventing ductal disease from becoming stromal disease, cystoprostatectomy with either adjuvant or neoadjuvant chemotherapy should be offered.

The EAU guidelines and WHO/SIU recommendations conclude that the data are insufficient to provide clear recommendations and, as there is no conclusive result regarding conservative therapy, a cystoprostatectomy should be considered in these patients.^{28,38} The NCCN guidelines consider both BCG with surveillance cystoscopies or immediate cystoprostatectomy as options.

Group 3: Prostatic Stromal Involvement (pT2–pT4)

Bladder cancer with concomitant prostatic stromal invasion technically is considered as a bladder cancer of a higher stage, T4a, and as such should not be considered as NMIBC. It should be treated with systemic neoadjuvant chemotherapy followed by cystoprostatectomy and urethrectomy according to most investigators

and guidelines,^{28,29,38} and thus is not discussed further here.

Evaluation of the Prostatic Urethra at the Time of Routine Cystoscopic Follow-Up of NMIBC

Studies looking at the follow-up of patients with NMIBC undergoing intravesical therapy (regardless of initial prostatic involvement) have identified prostatic involvement in 8% to 48% of cases.^{3,19,22–25} Herr and Donat³ followed 186 men with NMIBC for 15 years, and found prostatic recurrence in 72 patients (39%) after a median follow-up of 28 months. Of these, 27 patients (15%) developed stromal invasion. Similarly, Solsona and colleagues²⁵ followed 242 men with NMIBC with cold-cup prostatic urethral biopsies, of whom 32 had recurrence in the prostatic urethra. Despite additional TUR and intravesical therapy, 20 eventually re-recurred, with 13 progressing to bladder muscle or prostatic stromal invasion or distant metastasis, necessitating cystoprostatectomy, radiation, or chemotherapy. Schwalb and colleagues⁴² demonstrated that the prostatic urethra is the third most common site of recurrence at 16%, behind the bladder (64%) and ureter (20%), in patients who develop a positive urine cytology after having a complete response to BCG. Therefore, these investigators have recommended frequent random biopsies of the prostatic urethra at the time of routine cystoscopic follow-up, especially in the presence of bladder CIS or unexplained positive urine cytology.^{25,30,43} The aforementioned studies used 3- to 6-month intervals, but the optimal frequency of prostatic urethra biopsies has not been examined. The NCCN guideline recommends TUR biopsy of the prostatic urethra if cytology is positive, and when cystoscopy and imaging studies are negative, whereas the EAU and WHO/SIU do not address this issue specifically.

Management of the Urethra in a Patient with Prostatic Involvement Undergoing Cystoprostatectomy

Although most men with NMIBC can initially be treated with conservative therapy, there is a subpopulation of patients with refractory disease for whom cystoprostatectomy is indicated. Among the decisions that need to be made in choosing the best surgery for the patient is whether the urethra should be left in place. Urothelial cancer can recur in the urethra after cystectomy, contemporary series reporting a rate of 3.7% to 8.1%.^{44–47} Historically its prognosis has been poor, with median survival reported at 28 months, whereas

more recent series report 63% 5-year cancer-specific survival.^{46,48} In past decades it has been advised to perform urethrectomy at the time of surgery.⁴⁹ However, urethrectomy carries with it morbidity, including adverse effects on sexual functions,^{50,51} arguing for urethral sparing. Therefore, selectively performing urethrectomy on those men with a higher risk of urethral recurrence would prevent overtreatment with its associated morbidity. Reported risk factors include bladder CIS, upper tract urothelial carcinoma, tumor at the bladder neck, and involvement of the prostatic urethra.⁴⁷ The most consistent risk factor reported in studies is prostatic involvement, with 37% to 71% of those with urothelial carcinoma involving the prostate developing urethral recurrence after cystoprostatectomy.^{52,53} Of importance is that the depth of invasion affects the risk of recurrence. Urethral involvement (T1 or Tis pu) carries little risk of recurrence, ductal involvement (Tis pd) 10% to 25% risk, and stromal involvement 30% to 67% risk.^{52,53}

There is evidence suggesting that patients undergoing cutaneous diversion have a higher rate of urethral recurrence than those having an orthotopic neobladder.⁴⁶ A study by Freeman and colleagues⁴⁷ found 3% recurrence in patients with neobladders compared with 11% in patients with cutaneous diversion. Here again, prostatic involvement affected recurrence rates. Of men with urothelial cancer in the prostate, 5% of those who had a neobladder developed recurrence, as opposed to 24% of those who had cutaneous diversion.

One could conclude that this argues for preoperative TUR biopsy of the prostatic urethra before surgery. However, comparative studies have shown that intraoperative frozen section at the time of cystoprostatectomy is more accurate than TUR in predicting urethral recurrence. Lebreton and colleagues⁵⁴ reported a series of 118 cystoprostatectomy patients. Of these, 9 patients had positive TUR biopsies of the prostate, but negative urethral frozen-section margin. At 10 years of follow-up, none had recurred in the prostatic urethra. Cho and colleagues⁴⁴ found an 18-fold increase in risk of recurrence if urethral margins were positive.

EAU guidelines recommend urethrectomy if there are positive margins at the level of the urethra or any positive bladder margins, or if tumor extensively invades the prostate. Prophylactic urethrectomy is not justified.⁵⁵ The WHO/SIU conclude that urothelial carcinoma of the prostate diagnosed by TUR is not an absolute indication for prophylactic urethrectomy. Furthermore, a negative frozen-section of the prostatic urethra is

accurate in identifying patients at very low risk of developing a second primary or urethral tumor recurrence. However, a positive frozen-section should be considered a contraindication to performing an orthotopic neobladder.^{38,56}

SUMMARY

- In a male patient with NMIBC, urothelial cancer of the prostatic urethra can occur simultaneously or metachronously.
- The incidence is 6% to 37%, based on patient risk and diagnostic method.
- Tumor multifocality, CIS, and tumor involvement of the trigone and bladder neck have been associated with a higher risk of concomitant prostate involvement.
- Transurethral resection loop biopsy of the precollicular area between 5 and 7 o'clock will identify most prostatic urethral involvement.
- The presence of prostatic urothelial cancer may suggest understaging of an associated primary bladder tumor.
- The presence and depth of invasion of the prostatic urethra affects the prognosis and management.
 - Noninvasive papillary tumors and CIS of the prostatic urethra (T1 and Tis pu) carries the best prognosis, and can be treated with TUR and intravesical BCG and close follow-up.
 - Ductal urothelial carcinoma (Tis pd) has intermediate prognosis, and there is inconsistency between studies. Although TUR and intravesical BCG treatment has been described and is considered an option in the NCCN guidelines, cystoprostatectomy is commonly recommended.
 - Prostate stromal urothelial carcinoma (T4a) has the worst prognosis, and is treated with neoadjuvant therapy followed by cystoprostatectomy and urethrectomy.
- NMIBC managed conservatively can recur in the prostatic urethra at fairly high rates (8%–48%), often with stromal involvement. Some investigators recommend routine prostatic urethral biopsies.
- In patients undergoing cystoprostatectomy for bladder cancer with known prostatic involvement, a neobladder is an acceptable form of urinary diversion as long as a frozen section of the tip of the prostate is negative; in all other circumstances a urethrectomy should be performed.
- **Table 3** summarizes the recommendations from the various relevant guidelines.

Table 3
Summary of relevant guidelines/consensus

	EAU	NCCN	WHO/SIU
Indications for prostate biopsy for UCP	Bladder neck tumor, CIS present or suspected, positive cytology without evidence of tumor in the bladder, visible abnormalities of the prostatic urethra	Sessile bladder tumors, high grade cytology, suspicion of bladder CIS	—
Mode of diagnosis	TUR of precollicular area between 5 and 7 o'clock	TUR	—
Management of Tis pu and T1	TUR + intravesical BCG	TUR + intravesical BCG	TUR + intravesical BCG
Management of Tis pd	Cystoprostatectomy	TUR + intravesical BCG Or Cystoprostatectomy	Cystoprostatectomy
Management of T4 (stromal involvement)	Cystoprostatectomy	Cystoprostatectomy	Cystoprostatectomy
Follow-up biopsies of the prostate after BCG	—	Cytology is positive and cystoscopy and imaging studies are negative	—
Management of urethra at the time of cystoprostatectomy	Urethrectomy if: Positive margins at the level of the urethra, any positive bladder margins, tumor extensively invades the prostate	—	Urothelial carcinoma on TUR is not an absolute indication for prophylactic urethrectomy Negative frozen section accurate in identifying very low risk of urethra recurrence Positive frozen section is a contraindication for an orthotopic neobladder

Abbreviations: BCG, bacillus Calmette-Guérin; CIS, carcinoma in situ; EAU, European Association of Urology; NCCN, National Comprehensive Care Network; SIU, Société Internationale d'Urologie; TUR, transurethral resection; UCP, urothelial carcinoma of the prostate; WHO, World Health Organization.

Data from Refs. ^{28,29,38,55,56}

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The Costs of Non-Muscle Invasive Bladder Cancer

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KEYWORDS

• Bladder cancer • Cost-effectiveness • Quality of care

KEY POINTS

- Bladder cancer is the costliest cancer to treat in the United States on a per capita basis. Diagnosis, treatment, and continued surveillance all contribute to the economic burden of non-muscle invasive bladder cancer (NMIBC).
- Novel urinary markers are being investigated to replace cystoscopy and cytology in hopes of diminishing the burden associated with surveillance in NMIBC. Although showing promise, they currently lack the sensitivity and specificity to replace cystoscopy and cytology. In addition, the use of newer endoscopic methods such as fluorescence and narrow-band cystoscopy have yet to show superiority in detecting clinically meaningful lesions compared with traditional white-light cystoscopy.
- Characterization of the risk of recurrence and progression of patients with NMIBC can optimize surveillance strategies and lower expenditures associated with surveillance.
- The indirect costs of NMIBC include decreased productivity, reduced physical and social functioning, and a lowered health-related quality of life.
- Improved adherence to evidence-based practices such as recommendations for mitomycin C instillation, repeat resection of high-grade NMIBC, and induction bacille Calmette-Guérin would decrease the burden of NMIBC.
- Urologist-led quality collaboratives would likely improve on compliance with evidence-based recommendations and further optimize surveillance strategies in patients with NMIBC.

INTRODUCTION

Bladder cancer is one of the most common cancer diagnoses in the United States, with an estimated 68,810 new cases in 2010, accounting for 7% of all cancers and 3% of cancer deaths.¹ Approximately 70% of bladder cancers do not invade the underlying muscle at diagnosis²; this type of malignancy is broadly referred to as non-muscle invasive bladder cancer (NMIBC). Among NMIBCs, disorders can range from low-grade, superficial disease that often behaves in an indolent fashion to more aggressive high-grade lesions such as carcinoma

in situ (CIS) and lesions invading the underlying lamina propria. These high-risk, high-grade lesions have the potential to progress to muscle-invasive disease that is typically not amenable to the bladder-sparing treatments often used for NMIBC.

Treatment of bladder cancer is costly, in both direct and indirect terms. Of all cancers, bladder cancer is the ninth most costly in the United States in terms of overall expenditures,³ and has the greatest lifetime treatment cost per patient diagnosed, surpassing colorectal, breast, prostate, and lung cancers.⁴ Among the 5 commonest cancers in

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elderly patients, review of Medicare data expenditures also found bladder cancer to be the costliest.⁵ Of patients diagnosed with low-grade NMIBC, approximately 50% recur and 5% progress to muscle-invasive disease.² These recurrences necessitate multiple endoscopic resections and intravesical treatments combined with lifelong surveillance. Beyond the direct costs, NMIBC treatment also results in indirect costs such as lost productivity or the heightened psychological burden of a cancer diagnosis.

PATHOLOGY/STAGING

NMIBC is defined by the stage classification of the cancer according to American Joint Committee on Cancer (AJCC) specifications.⁶ Cancer grade is an important component of risk stratification within NMIBC. The World Health Organization (WHO) recently adopted the term urothelial cell carcinoma (UCC) to replace the traditional term transitional cell carcinoma.⁷ UCC was formerly graded from 1 to 3, with grade 1 lesions representing well-differentiated UCC and grade 3 lesions representing poorly differentiated UCC. However, as per WHO recommendation, this has been replaced by dichotomous histologic grading with UCC lesions now categorized as either high grade or low grade. This grading decreases some of the histologic discrepancy and interpathologist variability that was often present with grade 2 tumors with the earlier classification. Papillary urothelial neoplasm of low malignant potential (PUNLMP) and papillomas are two additional noninvasive bladder lesions that are rarely aggressive. PUNLMPs progress in fewer than 3% of cases; however, because of the possibility of local recurrence and the low probability of progression, many advocate maintenance of surveillance.⁸ Papillomas do not progress and do not require long-term follow-up.⁹

The bladder wall comprises 3 histologic layers. The inner urothelium is approximately 7 cell layers thick. Just deep to this, the lamina propria is a layer of blood vessels and lymphatics. The outermost muscularis propria predominantly functions to give the bladder its contracting ability. Stage classification Ta tumors are papillary tumors that do not extend deep to the urothelium. CIS (stage classification Tis) refers to a flat, high-grade lesion confined to the urothelium. Stage classification T1 tumors invade the lamina propria but do not extend into the underlying muscularis propria. This article focuses on the costs associated with management of lesions confined to the urothelium or lamina propria (ie, stage classification Ta, Tis, and T1), which are collectively referred to as NMIBC.

RISK FACTORS AND DEMOGRAPHICS

Tobacco smoking is the greatest known external risk factor for the development of bladder cancer. The relative risk among smokers for the development of bladder cancer is 2.8 in men and 2.7 in women compared with nonsmokers.¹⁰ This risk increases in proportion to a patient's duration of tobacco use and with the amount of tobacco exposure over time. Other environmental exposures also increase the risk for the development of UCC. Certain occupations with frequent contact with petroleum products, stains, and dyes have an increased risk for bladder cancer.¹¹ Such individuals include mechanics, leather workers, miners, and hairdressers.

Men outnumber women in bladder cancer diagnoses at a ratio of 3:1.¹² Although bladder cancer is more common in men, women often present with late-stage UCC, likely as a result of misinterpretation of presentation with hematuria. The incidence of bladder cancer increases with age; most diagnoses occur during the eighth decade of life. UCC is more prevalent in the white population, with white men and women having a 3-fold increase in the risk of developing bladder cancer compared with African Americans.¹³

DIRECT ECONOMIC BURDEN

The economic burden of diagnosis, treatment, and surveillance of NMIBC is substantial. Bladder cancer care in the United States in 2010 cost an estimated \$3.98 billion.³ Lifetime per capita costs have been estimated between \$96,000 and \$187,000 in 2001 US dollars, or more than \$230,000 in 2010 US dollars.⁴ Modeling patients whose course follows the best possible bladder cancer outcomes (patients with NMIBC with projected recurrences at the mean NMIBC rate), Avritcher and colleagues¹⁴ found that the lifetime cost of treatment of patients in a best-case scenario was \$120,684. Management of recurrences accounted for approximately 60% of this lifetime cost. If all patients newly diagnosed with NMIBC in the last year received recommended surveillance care with no recurrences (a perfect case scenario), the cost to the health care system for the management of this cohort for 5 years would exceed \$150 million.¹⁵

Several factors contribute to the cost of NMIBC. Most patients present with either gross or microscopic hematuria, and initial evaluation for hematuria consists of cystoscopy and cross-sectional imaging. Urine cytology is often performed to evaluate for CIS that may be difficult to visualize cystoscopically or to better define the anticipated grade

of identified bladder lesions. In instances of chronic kidney disease or contrast allergy, the expense of the initial evaluation is often compounded by the need to evaluate the upper urinary tract endoscopically, typically by performing retrograde pyelography or ureteroscopy under a general anesthetic.

If tumor or a suspicious lesion is visualized on initial cystoscopic examination, on radiographic examination, or if the urine cytology is suspicious for malignant cells, the initial tumor resection or biopsy of suspicious areas is usually done under general anesthesia. Intravesical instillation of mitomycin C is commonly indicated to reduce the risk of recurrence of bladder tumors, especially if the tumor seems to be low grade and noninvasive. For those diagnosed with NMIBC, the treatment and follow-up vary depending on the stage and grade of tumor. A repeat resection within 6 weeks is recommended for patients with high-grade T1 NMIBC disease because of a 64% risk of understaging when muscularis propria is absent from the initial resection and a 40% overall risk of understaging.^{16,17} Because management of upstaged NMIBC is different and cancer-specific outcomes suffer for mismanaged patients, repeat resection is not a candidate target for cost savings.

Following initial resection, among patients with high-grade NMIBC, intravesical bacille Calmette-Guérin (BCG) is typically indicated as first-line treatment. BCG is an attenuated mycobacterium that induces an immune response. Recommendations from the National Comprehensive Cancer Network (NCCN) advocate a 6-week induction course of BCG for those with high-grade Ta or T1 bladder cancer as well as those with CIS, followed by up to 3 years of maintenance therapy for multiple installations at varying time intervals,¹⁸ based on high-level evidence.¹⁹ Kilbridge and Kantoff²⁰ used a cost model to show that use of BCG in a 65-year-old man with high-grade NMIBC costs approximately \$4820 per year of life saved (2010 US dollars), a remarkable cost-effectiveness figure.

For patients with low-grade NMIBC, treatment and surveillance are less vigilant. Patients are often managed conservatively with surgical treatment of recurrences, without consideration of induction intravesical immunotherapy or chemotherapy. However, patients should receive a single instillation of intravesical chemotherapy concordant with resections, based on high-level evidence. Randomized trials and meta-analyses show that intravesical administration of mitomycin C given immediately after resection of a bladder tumor decreases tumor recurrence by approximately 35%.^{21,22}

For high-risk NMIBC refractory to treatment with BCG, salvage intravesical chemotherapy may help patients avoid major extirpative surgery, which is costly both in terms of expenditure and in the induced quality-of-life burden to the patient. Intravesical valrubicin has a single indication for its use as a salvage agent in high-risk NMIBC failing BCG. However, the cost-effectiveness of valrubicin for this indication may be marginally superior to that of radical cystectomy. Valrubicin showed durable benefit in 28% of patients with BCG-refractory NMIBC, and costs 6 times more than an induction course of BCG.²³ Cost-effectiveness models that incorporate the disutility of cystectomy with urinary diversion may better account for the benefit of salvage valrubicin.

Prediction algorithms have attempted to better classify patients' risks of recurrence and progression of bladder cancer to optimize surveillance strategies. The American Urological Association (AUA) categorizes patients into low-risk and high-risk groups based on grade and volume of cancer.²⁴ Low-risk patients have low-volume, low-grade NMIBC. Intermediate-risk patients have higher volume low-grade NMIBC. The AUA categorizes all patients with high-grade NMIBC as high risk. The NCCN describes a similar risk stratification classification, but the NCCN categorizes all patients with low-grade NMIBC as low risk, independently of tumor volume.²⁵ Intermediate-risk patients have high-grade stage classification Ta bladder cancer. High-risk patients with NMIBC have stage classification T1 and Tis tumors. The remainder of this article refers to the NCCN risk stratification and guidelines.

Patients with intermediate-risk or high-risk NMIBC require quarterly cystoscopies for the first 2 years after diagnosis with upper urinary tract evaluation every 1 to 2 years with cross-sectional imaging. Surveillance cystoscopy may be performed at increasing intervals if patients are recurrence free after 2 years. However, these patients are typically committed to a lifetime of upper tract surveillance. Although recommendations vary regarding surveillance for low-risk NMIBC, the presence of tumor at the initial 3-month cystoscopic evaluation is a prognostic marker for recurrent disease.^{26,27} NCCN guidelines recommend initial cystoscopy 3 months after resection, with subsequent cystoscopies at increasing intervals if the initial cystoscopy is negative for recurrence.¹⁸

Long-term surveillance of NMIBC contributes substantially to the cost burden of the disease. Compared with muscle-invasive bladder cancer, in which costs are disproportionately driven by initial diagnosis and treatment, complications of

these therapies and subsequent care, including end-of-life care, treatment complications account for only 4% of overall NMIBC costs.¹⁴ Because NMIBC surveillance mandates frequent invasive procedures and periodic cross-sectional imaging, these components of care dominate determinants of NMIBC costs. Changes in surveillance and treatment strategies have previously mirrored changes in physician reimbursement. In an effort to decrease the cost of hospital-based procedures, in 2005, Medicare adopted changes in reimbursements for office-based endoscopic procedures,²⁸ which led to a large increase in office-based procedures and increased the cost of NMIBC surveillance and treatment.

To mitigate the costs associated with cystoscopic surveillance, to address concerns about patient noncompliance because of procedural discomfort, and to overcome the low sensitivity of cytology, other novel urinary markers have been examined that could obviate cystoscopy. Cytology has a median sensitivity of 69% for the detection of high-risk tumors within the bladder, 78% sensitivity for detection of CIS, but lower sensitivity for upper tract lesions within the ureter and renal pelvis.²⁹ Thus, a negative cytology does not preclude cystoscopy, particularly in the setting of low-grade NMIBC or upper urinary tract tumors.

Commercial urinary markers for bladder tumor antigens (BTA stat and BTA trak) have superior sensitivity for low-grade tumors (48% vs 13% for cytology), but limited sensitivity overall, failing to detect 47% of tumors identified cystoscopically.³⁰ In addition, these tests had low specificity and frequent false-positive results in the setting of urinary tract infections. ImmunoCyt tests for markers of exfoliated UCCs. Similar to BTA stat and BTA trak, ImmunoCyt has improved sensitivity for low-grade NMIBC compared with cytology, but has low specificity. ImmunoCyt seems to be particularly confounded in patients with cystitis or benign prostatic hyperplasia.^{31,32} Urinary testing for NMP22 has sensitivity of 59%, 90%, and 70% for low-grade NMIBC, high-risk NMIBC, and CIS, respectively. Reduced sensitivity in cases of infection, bladder calculi, and prior urinary tract instrumentation curtail its usefulness in the evaluation and surveillance of NMIBC.^{33,34}

Fluorescence in situ hybridization (FISH) detects aneuploidy in chromosomes 3, 7, and 17, as well as loss of the 9p21 locus of the P16 tumor suppressor gene.³⁵ Sensitivity is limited in low-grade NMIBC, but increases in the detection of high-grade NMIBC.³⁶ FISH urinary testing does have some usefulness in patients undergoing treatment with intravesical BCG, a setting in which cytology has limited usefulness, and may be of

benefit in certain patients undergoing intravesical treatment who have ambiguous cytology results.³⁷ Kamat and colleagues³⁸ reported that high false-positive rates incurred with FISH tripled the cost associated with each additional cancer diagnosis compared with cystoscopy alone. To date, urinary markers have yet to be identified with adequate sensitivity or specificity to obviate cystoscopy and cytology and the potential cost reductions that could produce.

Novel endoscopic techniques have been developed to improve on detection of bladder cancer. Narrow-band imaging cystoscopy and fluorescence cystoscopy after intravesical instillation of 5-aminolevulinic acid or hexaminolevulinate have been shown to increase tumor detection rates compared with traditional white-light cystoscopy.^{39,40} Better detection was associated with decreased recurrence rates at 3-month surveillance, presumably because of complete treatment of all identified lesions at initial resection. Cauberg and colleagues³⁹ showed significantly decreased recurrence rates from 30.5% with conventional cystoscopy to 15.0% with narrow-band imaging cystoscopy 3 months after initial resection. A large multicenter study identified a 9% absolute reduction in the recurrence of bladder tumors using fluorescence cystoscopy.⁴⁰ However, these novel cystoscopic techniques are costly, and the proportion of lesions detected through fluorescence and narrow-band cystoscopy that are clinically important is unknown.

Management and surveillance of NMIBC remains costly. Unlike cancers that may be followed with serum laboratory tests or dedicated physical examinations, NMIBC requires expensive invasive procedures. Risk stratification can direct the intensity of surveillance required; patients with low-risk NMIBC can probably be followed less vigilantly than those with intermediate-risk or high-risk NMIBC. However, the investigation of other biomarkers for bladder cancer recurrence has not produced a test that has replaced the need for cystoscopy. Augmentation of conventional cystoscopy with new technologies has not shown convincing cost-effectiveness.

INDIRECT ECONOMIC BURDEN

Although the diagnosis, treatment, and surveillance of NMIBC consume substantial health care resources, there are indirect costs as well. Few studies have quantified the indirect costs of NMIBC treatment. The loss of work related to bladder cancer care can exert a major burden on patients. Patients with NMIBC undergo initial diagnostic evaluation, definitive biopsy in the operating

room, a possible repeat resection depending on the initial pathology, induction intravesical BCG, surveillance visits with cystoscopy every 3 months, the possibility of maintenance intravesical therapy, and additional time off depending on their threshold for recovery after each procedure. Among those who return to work is the probability of diminished productivity.

The socioeconomic profile of the average patient with bladder cancer suggests that loss of work could disproportionately affect those with NMIBC. Given primary risk factors of tobacco use and chemical exposure, professions associated with a bladder cancer diagnosis tend to be blue collar.¹¹ In contrast, because bladder cancer disproportionately affects older men and women, many patients with NMIBC are of retirement age and unaffected by work concerns. However, among younger patients yet to retire, the time from work required for NMIBC care could adversely affect their personal financial situation.

More awareness is being given to the psychological burden of bladder cancer and its treatment. Several health-related quality-of-life instruments have been validated for use in assessment of patient with bladder cancer, comprising questions pertinent to NMIBC and muscle-invasive bladder cancer care. The Bladder Cancer Index measures urinary, sexual, and bowel function and shows reliability among patients with muscle-invasive bladder cancer undergoing cystectomy and among patients with NMIBC.^{41,42} The Functional Assessment of Cancer Therapy Bladder Cancer (FACT-BL) similarly can be applied to patients with both muscle-invasive cancer and NMIBC but includes more generic quality-of-life questions.⁴³ The European Organization for Research and Treatment of Cancer (EORTC) likewise produced an instrument for quality-of-life assessment in NMIBC, the EORTC QLQ-BLS24.⁴⁴ The 24-item questionnaire is specific to patients with NMIBC and has questions devoted to the impact of intravesical therapy and cystoscopic procedures.

Applying these and generic quality-of-life questionnaires, several investigators have evaluated the outcomes of NMIBC survivors. Compared with age-matched and sex-matched controls, the mental health of patients undergoing resection was lower after the initial resection but eventually returned to normal on repeat resection.⁴⁵ Physical functioning, social functioning, and emotional quality of life were also lower among patients with NMIBC than among controls. Intravesical treatment with BCG also affects generic quality of life, irrespective of the cancer outcome, with increased psychological distress among BCG recipients.⁴⁶ Among bladder cancer-specific domains, a cross

section of patients with NMIBC showed superior urinary, sexual, and bowel function compared with patients with muscle-invasive bladder cancer following radical cystectomy.⁴² Patients who had received intravesical therapy had worse urinary function scores than patients with NMIBC who were naive to intravesical agents. Using FACT-BL, Allareddy and colleagues⁴⁷ showed similar disease-specific quality-of-life scores between patients with NMIBC and those having radical cystectomy, which may be a function of the generic nature of many FACT-BL items. Few studies have longitudinally evaluated patients with NMIBC to quantify whether resections, cystoscopies, or intravesical treatment courses have a cumulative impact on generic or bladder cancer-specific quality of life.

OPPORTUNITIES FOR IMPROVEMENT

The cost of health care in the United States currently accounts for approximately 17% of gross domestic product (GDP) and will increase to approximately 25% of the GDP by 2025. The expensive modalities of diagnosis, treatment, and surveillance of bladder cancer are potential targets for health care savings.⁴⁸ Diagnosis, predicated on imaging and cystoscopy, is unlikely to change. The domain of bladder cancer treatment could realize better cost-effectiveness. Despite level I evidence supporting instillation of chemotherapy after bladder tumor resection for prevention of cancer recurrence,²² review of practice patterns from population-based cohorts suggests that this may rarely occur in real-world practice.^{49,50} If accurate, this would be associated with marked harm to patients with NMIBC and to the health care system. Lee and colleagues⁵¹ estimated that 1025 quality-adjusted life years are lost in the United States every 2 years because of underuse of intravesical mitomycin C, which amounts to 8.1 quality-adjusted life days per patient. Because underuse of mitomycin C would be associated with an excess of more than 7800 recurrent NMIBC cases, better compliance could save more than \$30 million. Because a recurrence extends the need for frequent surveillance care, this study may underestimate the economic burden of underuse of postresection intravesical chemotherapy. The reduction in recurrences would also, almost certainly, reduce the psychological impact of NMIBC care.

Surveillance care represents a domain of bladder cancer care delivery with an opportunity to obtain better health care value. NMIBC surveillance guidelines are based on expert opinion. Studies of population-based practice patterns

show robust variation in adherence to these guidelines. Analyses using Surveillance, Epidemiology, and End Results (SEER) cancer registry data linked with Medicare claims (SEER-Medicare) have indicated that adherence to recommended NMIBC surveillance protocols may be very poor.^{50,52} Fewer than 40% of patients comply with a relaxed definition of recommended care.^{50,52} Applying more stringent criteria, almost no patients with high-risk NMIBC receive all recommended components of NMIBC care including repeat resection, induction BCG, and vigilant cystoscopic surveillance with cytology. The treating urologist affects patient compliance. Chamie and colleagues⁵⁰ found that 45% of the variance in compliance with NMIBC care is attributable to the treating clinician.

This appearance of noncompliance with guideline-recommended care may be a reflection of the lack of evidence underlying surveillance schedules. Hollenbeck and colleagues⁵³ critically evaluated the intensity of NMIBC surveillance using SEER-Medicare. The investigators found no difference in need for radical cystectomy or in survival outcomes for patients with high-intensity surveillance compared with patients with low-intensity surveillance. The investigators classified intensity by terciles of observed practice patterns, in which high-intensity care may still be noncompliant. To address this, a follow-up study stratified patients by the number of cystoscopic examinations and again found no difference in deaths from bladder cancer.⁵⁴ Current recommendations based on expert opinion may overestimate the needed burden of surveillance and tailored surveillance strategies could potentially lessen both the monetary and emotional costs associated with NMIBC follow-up. New technologies could guide surveillance schedules. Mutations in fibroblast growth factor receptor 3 (FGFR3) are common and have shown an association with less aggressive behavior than wild-type FGFR3 NMIBC tumors.^{55,56} Pending further studies, FGFR3 could be used to indicate patients in whom more relaxed surveillance strategies could be adopted. Decision analysis models comparing standard surveillance protocols with modified protocols informed by FGFR3 showed impressive cost savings with the modified schedule halving the expected costs for a standard protocol.⁵⁷ Other urinary biomarkers may similarly inform better risk stratification that could direct surveillance care.

In addition to the improvements in surveillance, more conservative treatment strategies might decrease operative resection of low-risk lesions. Low-grade tumors have a smaller chance of progressing to muscle-invasive bladder cancer than

high-grade lesions. Because the likelihood of progression is low, expectant management is an option for small lesions. Pruthi and colleagues⁵⁸ examined 22 patients with a history of low-grade NMIBC who underwent expectant management of their small papillary bladder tumors. At mean follow-up of 25 months, 17 had minimal growth and 5 had moderate growth of their tumors. Two patients required repeat resection because of tumor growth and worrisome cytology, both of whom showed grade or stage progression. Thus, expectant management is safe for patients with a known history of low-grade NMIBC who present with small-volume recurrences. Prospective studies may reinforce expectant management of small low-grade recurrences.

Because many of the quality detriments and clinical decisions that affect NMIBC costs are urologist driven, urologist-led quality improvement collaboratives have potential as a solution. For equivocal clinical situations, collaboratives can generate real-world comparative effectiveness estimates through transparent reporting of management outcomes and ascertainment of best practices. General surgical collaboratives have achieved remarkable cost savings for patients having bariatric and colorectal surgery with lower complication rates than regionally matched hospitals not participating in the collaboratives.^{59–62} Urologic collaboratives are already in operation. The Urologic Surgery Quality Collaborative⁶³ used practice feedback reports to reduce the overuse of advanced staging imaging studies for patients newly diagnosed with low-risk prostate cancer.⁶⁴ A similar initiative could address the underuse of intravesical chemotherapy after bladder tumor resection.

SUMMARY

Bladder cancer is a costly health condition. Because NMIBC is the predominant new bladder cancer diagnosis, understanding the drivers of the high cost of NMIBC care would identify targets for cost reduction initiatives and quality-improvement efforts. These costs affect the health care system, but the patient-centered costs of lost work, decreased productivity, and incurred quality-of-life detriments are similarly substantial. Ensuring better compliance with NMIBC treatments that are known to reduce recurrence rates could also reduce both direct and indirect costs. One emerging avenue for addressing compliance and the quality of bladder cancer care is urologist participation in clinician-led quality collaboratives, in which transparent reporting and benchmarking could affect the underuse of adjunctive NMIBC therapies.

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New Imaging Techniques for Non-Muscle Invasive Bladder Cancer: Ready for Primetime

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KEYWORDS

- Non-muscle invasive bladder cancer • Transurethral resection • White light cystoscopy
- Fluorescence cystoscopy • Narrow band imaging • Optical coherence tomography
- Confocal laser endomicroscopy

KEY POINTS

- Non-muscle invasive bladder cancer (NMIBC) is confined to the epithelium and lamina propria.
- Complete eradication and bladder preservation is the goal of transurethral resection (TUR).
- Technological limitations contribute to failure of TUR.
- Failure results in recurrence and progression.
- New imaging modalities that increase the urologist's ability to detect, stage, and treat NMIBC at TUR can have a significant impact in the treatment of NMIBC.

FLUORESCENCE CYSTOSCOPY

- Enhances tumor detection at initial resection for all stages and grades.
- Detection of carcinoma in situ is particularly enhanced with fluorescence cystoscopy (FC).
- Decreases rates of recurrence.

NARROW BAND IMAGING

- Shows similar efficacy in detection of tumors as FC.
- Does not require instillation of fluorophore in bladder before usage.

OPTICAL COHERENCE TOMOGRAPHY

- Provides real-time tumor grading during TUR.

CONFOCAL LASER ENDOMICROSCOPY

- Allows microscopic examination of urothelium in real-time for histopathologic analysis.

Bladder cancer remains one of the most difficult clinical conundrums for the practicing urologist. On the extremities of the disease, management of bladder cancer is simplified. The progressive nature of muscle-invasive disease dictates

definitive management and the gold standard remains radical cystectomy. At the other extreme, the likelihood of a single, subcentimeter, superficial (Ta) low-grade tumor progressing to muscle invasion is less than 1%.¹ Adequate management

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of such a lesion is eradication by transurethral resection (TUR) and a single instillation of intravesical chemotherapy at the time of resection. Recurrence and progression are monitored by quarterly cystoscopy for 1 year, decreasing in frequency thereafter if the patient remains free of tumor. Most patients, however, lie in between these 2 extremes. For these patients with non-muscle invasive bladder cancer (NMIBC), tumor recurrence and progression to muscle-invasive disease are a lifelong risk despite the multimodal application of chemotherapeutics, immune therapies, and repeated surgical resections.

Non-muscle invasive disease is confined to the epithelium (Ta) or the lamina propria (T1). A patient suspected of having bladder cancer undergoes evaluation with upper tract imaging, urine cytology, and cystoscopy.² The standard for evaluation of the lower urinary tract is white light cystoscopy (WLC), followed by TUR of any tumor that is discovered. Accurate assessment of histopathologic grade and depth of tumor invasion is required for the implementation of proper treatment. This implementation is accomplished by complete and accurate endoscopic resection at the time of TUR. For TUR to be successful, the tumor must be removed in its entirety, along with a sufficient margin of surrounding mucosae and the muscle directly beneath the tumor.²

WLC is, however, a technology fraught with deficiencies. Complete resection of papillary tumors is problematic and, as Brausi and colleagues³ demonstrated, often leads to early recurrence. As a result, a single TUR is often insufficient for the task. A repeat TUR, performed within 2 to 6 weeks of the initial TUR, shows residual disease a significant portion of the time depending on stage, grade, and tumor multiplicity. For pathologically confirmed disease confined to the epithelium (pTa), residual tumor is seen between 6% and 37% of the time.^{4,5} The rate is higher for disease that has been pathologically confirmed to invade into, but not through, the lamina propria (pT1) (33%–78%) and carcinoma in situ (CIS) (70%–80%)^{5,6} and incomplete resection is not the only limitation. High-grade Ta or T1 tumors are understaged 10% of the time even when muscle is present in the original resection specimen and will be found to be muscle invasive at re-resection. To what degree deficiencies of surgical technique contribute to this phenomenon is unknown. It is doubtless a factor, but there are also significant technological limitations that contribute to a surgeon's inability to eradicate a bladder tumor completely at the time of resection.

Further evidence supporting this comes from the difficulty of finding and eradicating CIS as

reported from trials that have recently explored the utility of random bladder biopsies. Despite the relative ease with which CIS is detected by bladder wash—fully 90% of patients with CIS are thought to have a positive cytology²—standard WLC fails to detect a lesion 50% of the time.⁷ CIS is a flat, high-grade noninvasive lesion that, unlike Ta and T1 disease, has a high potential for progression when left untreated.⁸ Classically described as a red “velvety” lesion, CIS is often multifocal and may be macroscopically invisible. Occult CIS is common when high-grade pTa or pT1 lesions have been identified and is present upward of 40% of the time.⁸

Of prognostic significance, CIS is, after tumor histopathologic grade, the second most important factor predicting progression to muscle invasive disease.⁸ Its detection is therefore paramount for accurate risk stratification and the implementation of treatment. Random bladder biopsies are often performed for just such a reason, as a random survey of the bladder mucosae for occult CIS. One recent study demonstrated random biopsies to be positive for CIS 8% of the time.⁹ Of clinical significance was the fact that, in a different study of random biopsying, random biopsies changed the indicated therapy 4.6% of the time.¹⁰

Finally, the economic impact of bladder cancer is immense. From diagnosis to death, bladder cancer is the most expensive cancer in the United States.¹¹ The inefficacy of cystoscopy for diagnosis and surveillance, in conjunction with the recurrent nature of the disease, is responsible for much of its financial burden. Technological advancements that can decrease recurrence have the potential to have a significant financial impact on health care costs if implemented properly.

FLUORESCENCE CYSTOSCOPY

The topical application of the protoporphyrin 5-aminolevulinic acid (5-ALA) was first performed in the early 1990s by a group of Munich urologists.¹² Before this, it had been shown that the intravenous injection of heme derivatives preferentially accrued in urothelial carcinomas.¹³ Heme derivatives are photoactive substances that absorb light at one wavelength and emit at another. Initially, the practical implementation of photodynamic tumor detection using heme derivatives, in particular porphyrin II, was attempted, but ultimately abandoned because of the systemic effects of skin photosensitization due to the porphyrins. Of practical importance, however, was the exposition that a photosensitizer could be used to enhance cystoscopy and tumor detection.

The Munich group, along with several other pioneering groups,^{14,15} showed that WLC could be effectively enhanced by the topical application of the protoporphyrin 5-ALA with minimal risk to the patient. Topical application managed to avoid the systemic complications associated with intravenous administration; however, the lipophilicity of 5-ALA still allowed for reasonably rapid local absorption over a period of several hours. These small proof-of-principle studies hinted, but were insufficiently powered to prove, that the instillation of 5-ALA before TUR could result in increased detection of all lesions and, in particular, 5-ALA had a distinct advantage in the enhanced detection of CIS. Subsequent randomized, prospective clinical trials would support these initial claims. 5-ALA has been consistently shown to enhance the detection of CIS greatly, with 33% to 36.7% more lesions detected.^{16,17} An advantage was also seen with the detection of pTa lesions and pT1 lesions, but it is not as pronounced (7%–11% and 3.6%–13%, respectively).

Enhanced detection at initial resection should lead to an increase in the rate of complete resection and a decrease of residual tumors seen at re-resection. Filbeck and colleagues¹⁸ demonstrated this in a randomized, prospective clinical trial. The WLC group had a 25.2% rate of residual tumor at 6 weeks, compared with 4.5% for the 5-ALA arm of the trial. On a stage-by-stage basis, the rate of residual tumor at 6 weeks for pTa was 17.8% and 3% for WLC and fluorescence cystoscopy (FC), respectively. pT1 had a greater rate of residual tumor for both, with the WLC arm having a rate of residual tumor of 36% and the FC arm having a rate of 11.8%. The difference was even greater when comparing residual CIS. In the WLC arm, CIS was found in 80% of patients at 6 weeks, whereas there was no residual CIS seen in the FC arm. This group also looked at the rate of recurrence in this trial and in a subsequent study

with an 8-year follow-up.¹⁹ The rate of overall recurrence for the WLC arm was 44% versus 16% for the FC arm. Further analysis based on risk stratification was also performed by this group. At 8 years there was a significant difference in recurrence-free survival (RFS) when comparing the FC arm to the WLC arm for all risk groups. The WLC group performed remarkably similarly regardless of risk stratification at 8 years (42%–45% for low, intermediate, and high risk stratification). The benefit of FC was greatest for low-risk patients (patients with solitary low-grade pTa or pT1 tumors), with 81% having no recurrence at 8 years. As tumor multiplicity and grade increased, however, the advantage narrowed but was still significant. The intermediate-risk group had the same grade and stage as the low-risk group, but presented with multiple tumors initially, which resulted in an RFS of 70% in the FC arm at 8 years. High-grade disease, including CIS, conferred additional risk of recurrence at 8 years. Nonetheless, 60% of patients remained recurrence-free in the high-risk group.

Further refinements have resulted in hexamino-levalinate (HAL)—Hexvix in Europe (Photocure ASA, Oslo, Norway) and Cysview in North America (Photocure USA, Princeton, NJ)—largely supplanting 5-ALA as the protoporphyrin of choice. HAL is a hexyl ester derivative of 5-ALA. It is significantly more potent than 5-ALA due to its increased lipophilicity and tissue solubility. This increased lipophilicity and tissue solubility allow for decreased instillation time and surgeon convenience for practical usage during TUR without any increase in its complications. Like 5-ALA, HAL absorbs blue light (wavelength 380–480) and emits red light (**Fig. 1**). Polarized light filters allow for visual enhancement of a tumor that appears red on a dark blue background.

Stenzl and colleagues²⁰ have shown similar results with HAL in an international randomized,

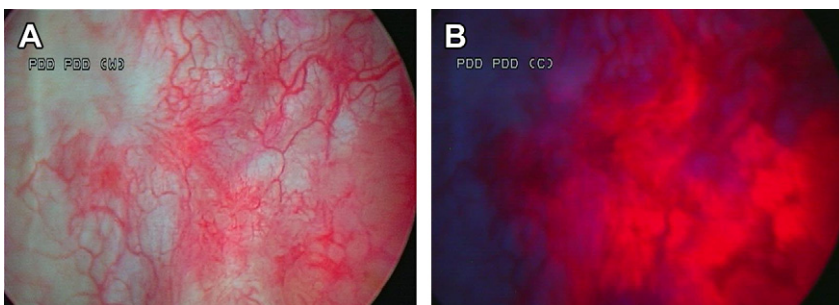


Fig. 1. (A) White light cystoscopy of a CIS lesion. Perception of lesion is limited to hypervascularity and subtle yellowish pigmentary discoloration of mucosae. (B) Fluorescent cystoscopy of the same lesion. The red enhancement of the tumor is not limited to identification but also extends the boundary of the lesion to be resected.

prospective trial that compared WLC-based and HAL-based FC. In this study there was a 32% increase in the detection of CIS in the fluorescence arm. Moreover, enhanced detection of tumors that were clinically relevant was also noted in this trial. The patients in the WLC arm underwent white light interrogation only, whereas the fluorescence arm group underwent an initial white light examination that was then followed by blue light interrogation. Tumors were mapped at both times and the results were recorded. In the fluorescence arm there was a 16% increase in the number of lesions detected. Of these lesions, 41% were high-grade Ta or T1 lesions that would not have been detected by WLC alone. This group also looked at rates of recurrence in a subsequent study.²¹ The time to recurrence was significantly improved in the fluorescence arm when compared with the white light-only arm (16.4 months vs 9.4 months, respectively).

A further advantage that FC has over standard WLC is its ability to more accurately demarcate tumor from normal mucosae and aid in the complete resection of a tumor that is visible with both modalities. A single-center prospective, randomized trial by Geavlete and colleagues²² found that 8.5% of tumors that had been resected under WLC had pathologically confirmed positive margins that could be visualized by FC (Fig. 2). This group also showed in a subsequent study that at the time of initial resection FC was superior in detecting multiple tumors when compared with WLC (35.2% vs 14.1%, respectively).²³ Furthermore, their analysis showed that HAL-based FC modified the risk stratification and the postoperative treatment regimen in several patients and aided a more accurate pathologic classification. Of particular note, patients who would have been declared “tumor free” by WLC, but the addition of HAL resulted in increased detection of bladder tumor.

Stated another way, at initial TUR, there was a failure to find a tumor—the patient was “tumor-free”—7.7% of the time. In the FC arm, only 1.4% of patients were designated “tumor-free.”

Not all studies to date have shown a uniform advantage of FC over WLC. Schumacher and colleagues,¹⁶ in a randomized, multicenter, prospective trial, failed to show any advantage with respect to rates of recurrence for FC over WLC. An overall advantage for FC was seen in tumor detection and was consistent with other published trials—33% advantage in detecting CIS, 13% for pT1, and 6.7% for pTa—but no advantage was seen in rates of recurrence at 12 months in either low-risk or high-risk patients. One factor that could contribute to the difference seen in this trial is that it was a multicenter study. As a result, some of the surgeons who performed the TUR resections had limited experience with FC before their inclusion in the study.

Criticisms of HAL and 5-ALA are primarily twofold. One concern is its lack of specificity and high false-positive rate. The other concern is that neither influences disease progression and the number of individuals who progress to muscle-invasive disease is unchanged. Nonspecific uptake of heme derivatives does occur. This nonspecific uptake of heme derivatives is most notable in patients with a prior history of TUR and bacillus calmette-guerin (BCG) therapy. Inflammatory lesions, scars, and granulomas can all appear as red lesions on a blue background, the same as an FC-positive bladder tumor. Initial studies reported false-positive rates for FC as high as 51%.²⁴ However, the inability to diagnose strictly based on appearance is not unique to FC and false-positive biopsying occurs in even in the most experienced hands under WLC. Most recent large prospective, randomized trials have similar rates for false-positive biopsying (10%–15%) regardless

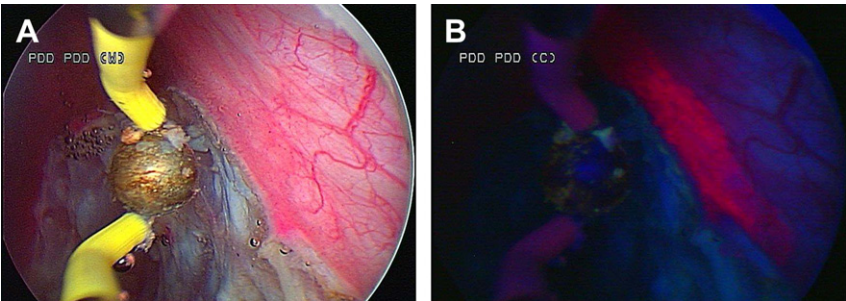


Fig. 2. (A) The bed of a papillary lesion that has been completely resected by WLC. Customarily, it is the authors’ practice to extend the margin of the resected tumor to ensure complete resection of the tumor. (B) Reexamination of the tumor bed by fluorescent cystoscopy reveals a positive margin. Tumor resection margin was extended at the time of the resection accordingly.

of the modality directing the biopsy, with a slight increase of 1% or 2% for blue light-directed biopsies.^{17,23}

With regard to progression, FC-based cystoscopy has not been conclusively shown to improve progression-free survival. Stenzl and colleagues²⁰ found no difference between the 2 arms, whereas others have shown a modest improvement of 1% or 2%, but these were not statistically significant.^{16,23}

Several studies have looked into the cost-effectiveness of fluorescence-based cystoscopy. Stenzl and colleagues²⁵ first looked into the cost-effectiveness of 5-ALA and found that the savings could be substantial if the difference in the rate of recurrence was 20%. The savings were largely due to avoided TURs. This savings covered the added expense of the supplemental equipment needed for FC by a factor of 3. Danilitchenko and colleagues²⁶ also found a significant cost-savings based primarily on the decrease in the total number of TURs that would need to be performed. Most convincingly, Zaak and colleagues²⁷ performed a cost analysis on a per-patient basis and analyzed patients who had undergone WLC and FC. They found a savings of about \$250 per patient per year over a 7-year follow-up.

NARROW BAND IMAGING

The propensity of bladder cancers to be hypervascular is exploited in narrow band imaging (NBI). White light emanating from the lamp source is filtered into 2 discrete wavelengths—415 (blue) and 540 (green)—that have only superficial tissue penetration. Correspondingly, these are the peak absorptive ranges for hemoglobin. When combined with high-resolution magnifying endoscopy, the vascular architecture of a bladder lesion is

accentuated and the disparity between malignant and benign is heightened. The technology was initially used for the characterization of colonic lesions^{28,29} and was adapted to the cystoscope shortly thereafter.²⁸ Vascular structures appear dark brown (capillaries) and green (veins) on a pink-white background (normal mucosae) (Fig. 3). Unlike fluorescence cystoscopy, it does not require the instillation of a photoactive substance. Likewise, it avoids the added costs of the porphyrin and time associated with its instillation, and is more convenient to implement.

Initial studies have shown comparable efficacy to FC with regard to CIS, Ta, and T1 disease detection. Geavlete and colleagues,³⁰ in a single-center, prospective trial where patients were interrogated under WLC and then NBI, found a 33% difference in rates of detection for CIS in favor of NBI. pTa and pT1 also had increased rates of detection of 8.7% and 10.9%, respectively. This increased detection of tumors by NBI resulted in therapeutic augmentation in 10.6% of the patients where additional lesions were detected. Cauberg and colleagues³¹ found a similar increase in total detection for NMIBC. Although their study tended to have low-grade disease and lower rates of CIS, 28 of 79 patients who were eventually diagnosed with NMIBC had additional lesions found by NBI. Conversely, WLC detected lesions that were not seen with NBI in only 3 of 78 patients. Of note, in this study the prevalence of CIS was 10.6%. NBI and WLC failed to detect CIS in 18% of the patients diagnosed with CIS and in these cases random biopsies were responsible for detection. Further studies that compare NBI with FC directly will be needed to determine which modality is superior for the detection of CIS.

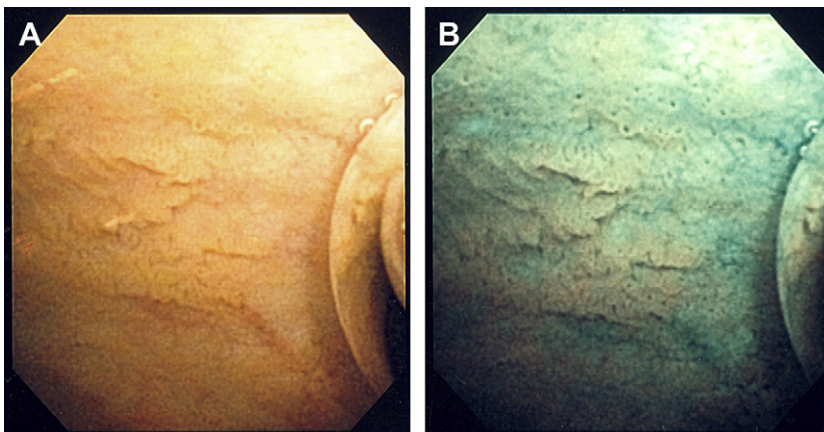


Fig. 3. (A) White light cystoscopy of a bladder tumor at the dome of the bladder (air bubble on the right side of the frame). (B) Enhanced contrast of tumor relative to WLC with brown tumor on green/white background.

Naselli and colleagues³² analyzed NBI superiority to WLC during a second-look TUR in patients with high-grade NMIBC at 1 month. In this prospective observational study, patients underwent a second-look TUR under WLC first and then were interrogated for the first time by NBI. In all, 34% of patients had pathologically confirmed residual disease during the second-look TUR. Approximately one-third of these patients had lesions that were missed by the 2 TURs under WLC, but were detected by NBI. This same group also assessed rates of recurrence in a prospective, randomized trial.³³ NBI had 19.8% fewer recurrences at 1 year when compared with WLC. Similarly, Herr and Donat³⁴ found an RFS of 29 months versus 13 months for NBI and WLC, respectively, in patients with low-grade disease.

Early studies have shown high rates of false-positive biopsying, but this has not been borne out by later trials. This pattern is similar to what was observed in the early trials with HAL and 5-ALA. Herr and Donat³⁵ and Cauberg and colleagues³¹ both reported a false-positive rate of biopsy of 36% and 31.6%, respectively, for NBI. Geavlete et al, in a recent prospective trial, had false-positive rates of 13.6% versus 11.5% for NBI and WLC, respectively.³⁰

OPTICAL COHERENCE TOMOGRAPHY

Several new technologies allow for real-time, microscopic evaluation of the bladder mucosae. Optical coherence tomography (OCT) provides a cross-sectional image similar to an ultrasound, but uses near-infrared light instead of sound waves. Use of near-infrared light allows for increased resolution relative to high-frequency ultrasound. With a depth of penetration of 1 to 3 mm, the epithelia, lamina propria, and muscularis propria are readily identifiable. The corresponding layers have a different scatter and appearance. Tumors appear as disruptions in the tissue planes. A fiberoptic-based technology, OCT is adaptable to a rigid or flexible WLC and is used as an adjunct means of microscopic interrogation of the urothelium and underlying microarchitecture. Virtual tumor grading is performed by the surgeon in real-time during a TUR.

Early prospective studies have shown the significant limitations of early iterations of this technology. Karl and colleagues³⁶ were able to identify and stage all lesions correctly that were detected by WLC, but had an exceedingly high false-positive rate. Of 102 lesions identified by WLC and interrogated by OCT, 45 were suspected to be malignant by OCT. Malignancy was confirmed by biopsy on only 14 of these lesions.

Encouragingly, there were no false negatives. Virtual histopathologic analysis was limited to tumor stage as the fidelity of the device did not allow for tumor grading. Device resolution in these early trials was 10 to 20 μm and depth of tissue penetration was limited to 2 mm. Recent advancements have increased resolution to submicrometer levels and are integrating Doppler and enhanced 3-dimensional imaging.³⁷ Furthermore, integrative software has been added to mitigate diagnostic subjectivity. Promising work has been performed by Ren and colleagues³⁸ in a transgenic mouse model for CIS. This group has additionally used OCT in conjunction with other imaging modalities (eg, WLC, NBI, and FC). The early results are promising for the combined use of OCT with both FC and NBI; however, further studies in humans will need to be performed as the applicability of the transgenic mouse model is not known.

CONFOCAL LASER ENDOMICROSCOPY

Confocal laser endomicroscopy (CLE) is another modality that, like OCT, is capable of examining the urothelium on a subcellular level. Fiberoptic advancements have allowed the conventionally bulky confocal laser microscope to be miniaturized and adapted to the working channels of endoscopes. Currently, it is approved for use within the respiratory and gastrointestinal tracts with promising results, particularly in identifying precancerous lesions in the esophagus.³⁹ Probes have been developed that accommodate both rigid and flexible cystoscopes. CLE does require administration of a fluorescent contrast agent, fluorescein, which has long been used by ophthalmologists and has an excellent safety profile when used optically and in the gastrointestinal tract. In the lower urinary tract, fluorescein is administered intravenously and/or intravesically. Fluorescein stains the extracellular matrix and penetrates the lamina propria regardless of whether it is administered intravenously or intravesically. It does not, however, allow visualization of nuclei or the muscularis propria. Wu and colleagues⁴⁰ compiled an atlas of upper and lower tract lesions and found a distinct profile for normal, inflammatory, and malignant lesions. The reproducibility and widespread applicability of CLE are currently unknown and further studies are needed.

DISCUSSION

Tumor multiplicity is the single greatest prognostic factor that influences cancer recurrence.⁸ The enhanced ability to detect more tumors at initial resection and more accurately assess the

boundary between normal mucosae and malignancy allows for a more complete resection at TUR and an increase in time to recurrence. Both NBI and FC have shown superiority with respect to WLC alone in tumor detection for all stages. The most pronounced advantage is with respect to the detection of CIS. Further trials will be needed to elucidate which method is superior.

NBI has the added advantage of not requiring instillation of contrast media. Not requiring instillation of contrast media avoids the costs of the contrast and associated disposables as well as the man-hours associated with its instillation. A similar advantage exists for OCT relative to CLE.

It should be reiterated that all the technologies mentioned in this article are meant to be used as an adjunct to WLC and are not meant to supplant WLC. As illustrated by Cauberg and colleagues,³¹ NBI had a distinct advantage in CIS detection, but in approximately 4% of patients lesions were detected by WLC that were not seen by NBI. Furthermore, the addition of NBI or FC to WLC will not obviate random biopsies as persistent, occult CIS will not be eradicated by the universal adoption of either. The prevalence of occult CIS should decrease, but further studies are needed to define the advantage.

The addition of OCT or CLE has the potential to aid in enhancing the real-time accuracy of histopathologic analysis. This addition of OCT or CLE in turn could result in a decrease in pathologic specimens requiring processing and possibly even complication rates for TUR, but it will not likely influence rates of recurrence as the technologies currently exist. The field-of-view for both is limited. Furthermore, the lesion is still identified by WLC, or if used concurrently with NBI or FC, by those modalities. OCT and CLE are therefore dependent on those technologies for the identification of lesions. Universal interrogation of the bladder mucosae is not practicable by either OCT or CLE. Further limitations of OCT and CLE are the need for direct apposition of mucosae and device for use, proving untenable in certain areas of the bladder like the anterior bladder neck and posterior dome.

Progression and bladder preservation have not been conclusively shown to be affected by either FC or NBI. The greatest prognosticator of progression is tumor grade.⁸ High-grade disease and, in particular, concomitant CIS carry a significant risk of progression.⁴¹ Although FC and NBI greatly enhance the capability of WLC to detect CIS, and FC has been shown to more accurately demarcate tumor boundaries, the sensitivity of either modality is not absolute. Occult disease will persist in a minority of patients and progression can then

occur. Larger trials are needed that compare NBI and FC and may be able to show an influence on progression.

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Diagnostically Challenging Cases: What are Atypia and Dysplasia?

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KEYWORDS

• Bladder • Urothelial carcinoma • Atypia • Dysplasia • Pathology

KEY POINTS

- *Atypia* and *dysplasia* are terms used to describe cellular abnormalities in the spectrum of reactive changes to neoplasia.
- Acute and chronic inflammation secondary to infectious, mechanical, or idiopathic causes can induce cytologic and architectural changes that can be interpreted by pathologists within the spectrum of atypia.
- Treatments, including systemic chemotherapy, intravesicular therapy, and radiotherapy, incite specific, often common, cellular changes that can microscopically be concerning for a neoplastic process.
- Despite improved investigation, the utility of immunohistochemistry as an ancillary tool in distinguishing benign processes from urothelial neoplasia remains unclear.

INTRODUCTION

The urothelial lining of the bladder presents diagnostic challenges, even under normal circumstances. A multitude of confounding factors, such as inflammation, reparative changes, distension state, and treatment effects, can hinder a diagnosis of early neoplasia. Thus, evaluation of biopsy and/or transurethral resection specimens requires pathologists to command a detailed understanding of the spectrum of histologic changes that can arise in the urinary bladder. Adding to the diagnostic challenge is that available ancillary studies, such as immunohistochemical (IHC) stains, are suboptimal in the diagnosis of bladder neoplasia. In light of these difficulties, pathologists have developed several diagnostic categories to address the histologic gray zones in bladder pathology. Despite what progress has been made, these categories are subjective and often do not correlate with outcomes.

WHAT ARE ATYPIA AND DYSPLASIA?

The definition of atypia has been a contentious topic within the field of pathology, not restricted to the genitourinary subspecialty. The lack of consensus on one of the most commonly used terms in pathology can be attributed to a variety of causes, such as the subjective nature of histologic evaluation, institutional bias, prior diagnosis, and preference of the evaluating pathologist.¹ Furthermore, some pathologists have used the terms, *atypia* and *dysplasia*, interchangeably, which can introduce problems in clinical management. It is implied that atypia represents a benign process in many instances whereas dysplasia describes a preneoplastic/neoplastic process,¹ although variation in defining these categories at the microscopic level often leads to confusion.

From a histologic perspective, atypia refers to a presence of 1 or more cellular or architectural features that deviate from that of an otherwise

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normal-appearing cell or group of cells. Under normal conditions, urothelial cells contain oval nuclei, finely stippled chromatin, and minute to absent nucleoli as well as ample cytoplasm and distinct cell membranes (**Fig. 1**).² Even within the spectrum of normal, urothelial cells are permitted to have certain variations in cell size and cytoplasm, particularly in the most superficial layer of the urothelium (umbrella cell layer), which is in constant contact with the contents of the urinary space. These umbrella cells tend to be larger than cells in the intermediate and basal layers, with occasional binucleation and abundant eosinophilic cytoplasm. To further complicate matters for pathologists, bladder distension can lead to flattening of superficial (or umbrella) cells to a point where the layer can be difficult to identify microscopically.³

Despite the variety of appearances of normal urothelial cells, certain specific cellular features are evaluated when determining the presence of atypia. Abnormal nuclear features, including increased size (nucleomegaly), deviation from typical ovoid shape, coarse chromatin, and irregular nuclear membrane contour, are all contributory factors in classifying cells as atypical (**Fig. 2**).⁴ In addition, the identification of an enlarged, prominent nucleolus or multiple nucleoli should raise concern.¹ Although eosinophilic (pink-appearing) cytoplasmic features are acceptable in the superficial urothelium, these cytoplasmic changes in other layers, as well as loss of cytoplasmic clearing, are also considered atypical features.⁴

Although atypia often refers specifically to cytologic (cellular) abnormalities, architectural changes can also guide pathologists to the appropriate

diagnosis. Denudation of the urothelium can be associated with previous instrumentation, inflammation, or a neoplastic process (**Fig. 3**).⁵ Conversely, thickening (hyperplasia) of the epithelium can result from a variety of causes, ranging from a benign proliferation to a reactive process secondary to inflammation, as well as being simply an artifact of tangential sectioning.⁶ The presence of atypical cells in the background of varied epithelial thickness can pose a difficult diagnostic challenge. Assessment of histologic changes throughout the entire specimen, detailed clinical history, and cystoscopic findings are all necessary to ensure that correct diagnosis is made. As such, close communication with the treating urologist is critical for the appropriate diagnosis and management of a patient.⁷

DIAGNOSTIC CATEGORIES OF FLAT UROTHELIAL LESIONS

Reactive Urothelial Atypia

Reactive urothelial atypia remains one of the broadest categories used to describe abnormal-appearing urothelium but is generally considered at diagnosis to represent a benign process.⁵ Reactive atypia is most often diagnosed in the setting of an acute and/or chronic inflammatory process that may arise in the setting of past instrumentation, infection, prior treatment, and other clinical scenarios that incite inflammation. The cytologic and architectural abnormalities that arise in these contexts are generally mild and uniform.⁴ Increased nuclear size, vesicular-appearing chromatin, and pinpoint nucleoli are the most common features identified microscopically with reactive

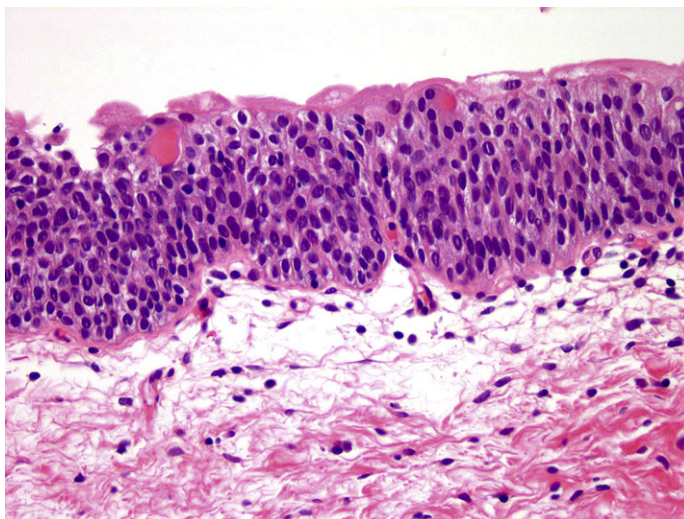


Fig. 1. Normal urothelium (hematoxylin-eosin, original magnification $\times 20$).

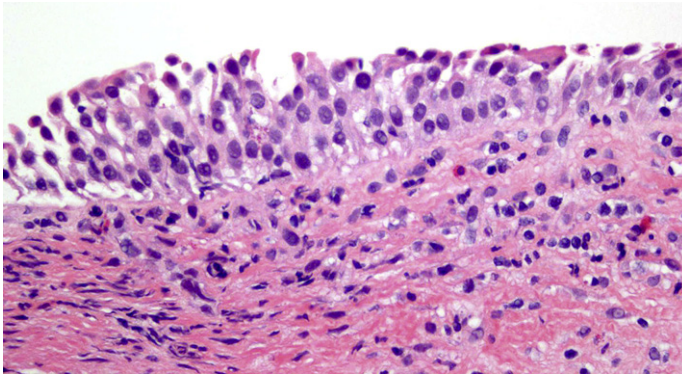


Fig. 2. Atypia demonstrates subtle changes from normal, which may include occasional hyperchromasia, disorganization, or increased nuclear/cellular variability (hematoxylin-eosin, original magnification $\times 20$).

changes, which often occur in the presence of an inflammatory infiltrate within the urothelium (Fig. 4).¹ A key distinction for reactive atypia is uniformity of findings throughout the specimen. Pleomorphism (variation in nuclear size), hyperchromasia, and nuclear crowding are features that should raise concern for a probable preneoplastic or overt neoplastic process.⁸

Atypia of Unknown Significance

Atypia of unknown significance is a term introduced by an International Society of Urological Pathology consensus group in 1998¹ to classify histologic findings that meet various criteria for both reactive changes and dysplasia. Typically, this diagnosis is used in the setting of reactive nuclear and cytoplasmic changes with mild degrees of pleomorphism and/or hyperchromasia that are concerning for dysplasia. Additionally, this term has been used to describe histologic findings where the level of atypia is disproportionately

greater than expected for the amount of inflammation. There is ongoing debate on whether this term is even an appropriate diagnosis.⁴ The classification of histologic findings as atypia of unknown significance warrants clinical follow-up, ideally in the setting of resolved inflammation. Despite the inclination to monitor these patients prospectively, there is no evidence in the literature that has shown that this category of patients is predisposed to neoplastic progression, although further studies are needed to better clarify this entity.⁸

Urothelial Dysplasia

Urothelial dysplasia is considered to represent early preneoplastic/neoplastic change, with histologic features beyond those considered in the spectrum of benign or reactive urothelium.⁹ In dysplasia, the thickness of the urothelium can be variable, but umbrella cells are usually present. Features of cellular crowding, multiple nucleoli,

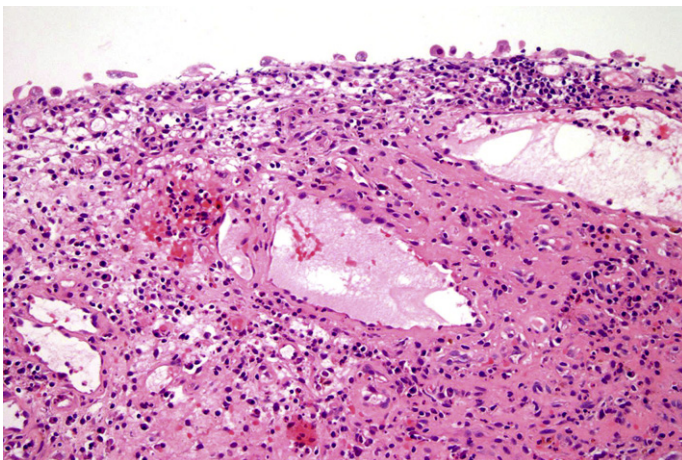


Fig. 3. Denudation may lead to a diagnosis of atypia (hematoxylin-eosin, original magnification $\times 10$).

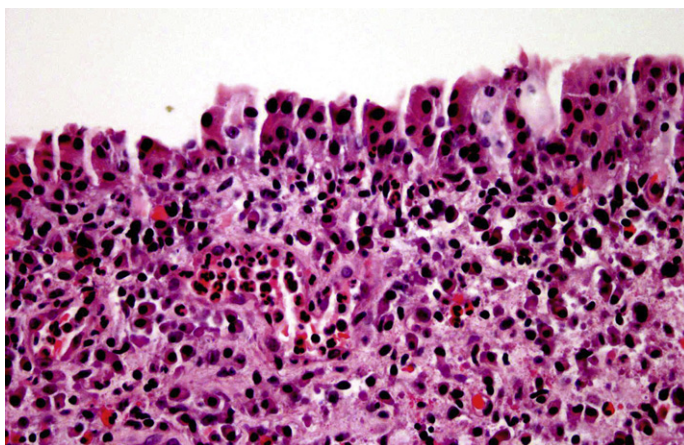


Fig. 4. Inflammation may complicate diagnostic accuracy, often leading to a diagnosis of atypia (hematoxylin-eosin, original magnification $\times 20$).

and mild hyperchromasia are common in this diagnostic category (**Fig. 5**).¹⁰ The diagnosis of dysplasia is used when some, but not all, of the criteria necessary for urothelial carcinoma in situ (CIS) are met. Currently, further subclassification of dysplasia as mild grade or moderate grade is no longer commonplace, whereas severe dysplasia is generally considered CIS.

Urothelial dysplasia can be further categorized into primary (de novo) and secondary dysplasia. Primary dysplasia is defined as dysplasia occurring in the absence of other histologic features of CIS and with no precedent history of urothelial neoplasia.⁸ Because patients are usually asymptomatic and/or no gross lesion is visible on cystoscopy, true primary dysplasia is rarely seen by pathologists. Secondary dysplasia is classified as

dysplasia identified in the setting of known neoplasia of the bladder, either current or prior. In either presentation, patients are currently undergoing screening to assess current symptoms or monitoring of a precedent high-grade lesion. Although both primary and secondary dysplasia are classified as true premalignant lesions, secondary dysplasia is more likely to progress to carcinoma.⁸

Carcinoma in Situ

Urothelial CIS is a neoplastic diagnosis, with malignant cells restricted within the urothelial lining of the bladder (noninvasive disease). In addition to the features of dysplasia, these cells demonstrate marked nuclear and cellular pleomorphism and

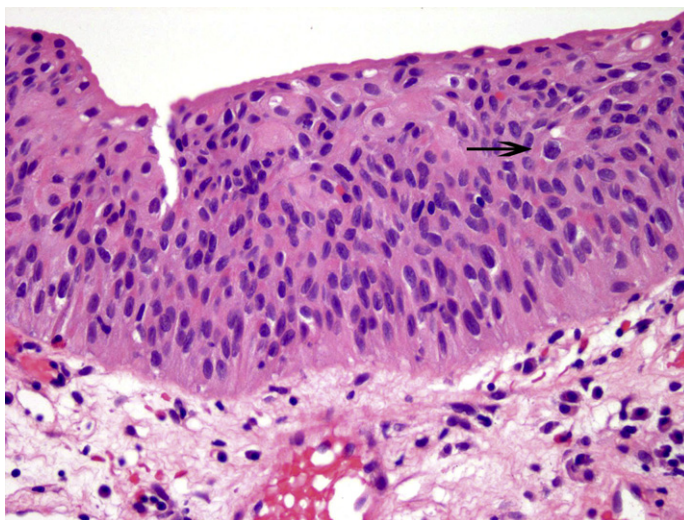


Fig. 5. Dysplasia is a subjective diagnosis. In this case, variable nuclear size, mild cellular disorganization, and occasional abnormal nuclear contours (*arrow*) support the diagnosis (hematoxylin-eosin, original magnification $\times 40$).

hyperchromasia (**Fig. 6**).⁹ CIS is commonly underdiagnosed when full-thickness cytologic atypia is absent or when umbrella cells are identified. Underdiagnosis of CIS may also occur in the setting of clinging CIS (single carcinoma cells are present in a background of otherwise denuded urothelium) and subtle involvement of von Brunn nests by CIS cells.⁹

INFLAMMATION AS A CONTRIBUTOR TO A DIAGNOSIS OF ATYPIA/DYSPLASIA

There are many inflammatory and infectious processes that incite reactive changes within the urinary bladder. Specifically, acute and chronic inflammation secondary to infectious, mechanical, or idiopathic causes can induce cytologic and architectural changes that can be interpreted by pathologists within the spectrum of atypia. The following categories represent a sampling of some of the common inflammatory processes that often lead to a diagnosis of atypia and/or dysplasia on bladder biopsy.

Acute and Chronic Cystitis

The most common cause of acute cystitis is infection, primarily, but not restricted to, gram-negative bacteria.¹¹ Additional causes of acute cystitis include prior instrumentation, trauma, and catheterization. In the acute setting, inflammatory-mediated cell responses lead to an influx of neutrophils, lymphocytes, and macrophages within the urothelium and lamina propria of the bladder. Edema and vascular congestion are also common.¹² Although reactive changes of the urothelium may not occur until the subacute or

chronic inflammatory phase, pronounced inflammation can obscure underlying pathologic processes and make assessment difficult for pathologists, thus leading to a diagnosis of atypia. In the setting of chronic cystitis, a variety of changes can occur in the urothelium, including denudation, ulceration, or hyperplasia. In addition to difficulties in adequately visualizing the specimen microscopically secondary to copious amounts of granulation tissue and/or fibrosis, reactive atypia due to a persistent inflammatory process can raise suspicion for dysplasia in the bladder.⁸

Polypoid Cystitis

Polypoid cystitis, a common variant of cystitis in the bladder, remains a challenging inflammatory lesion for pathologists and urologists alike (**Fig. 7**).¹³ On cystoscopy, the often exophytic growth pattern of polypoid cystitis may clinically resemble a papillary neoplasm. These lesions tend to appear in patients with a history of indwelling catheters, fistulas, chronic obstruction, or calculi. Microscopically, the lesion consists of large, bulbous outpouchings of the urothelial lining, with the lamina propria often edematous (**Fig. 8**).¹³ Over time, ongoing inflammation may produce scarring of the lamina propria, leading to a more papillary-like appearance as well as inducing squamous metaplasia and reactive atypia.¹⁴ In a 2008 study, 41 cases of polypoid cystitis previously misdiagnosed as papillary urothelial neoplasia were rereviewed.¹³ Despite some mild atypia and mitotic figures in many of the cases, the cytologic features included uniform cell enlargement, similar vesicular chromatin patterns,

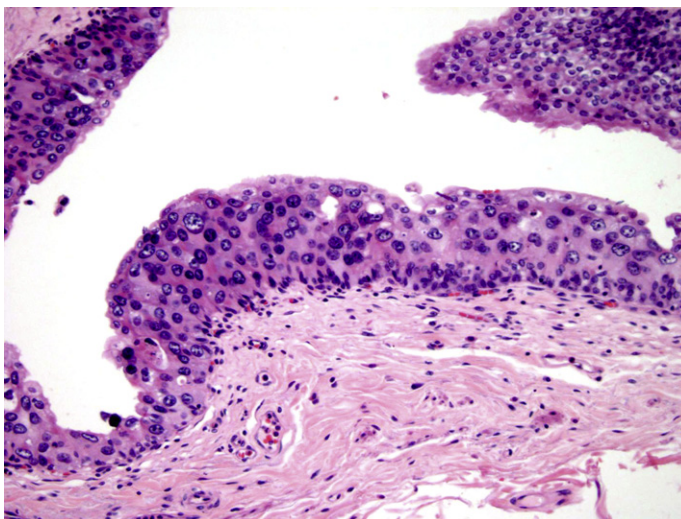


Fig. 6. CIS typically shows overt neoplastic features (hematoxylin-eosin, original magnification $\times 20$).

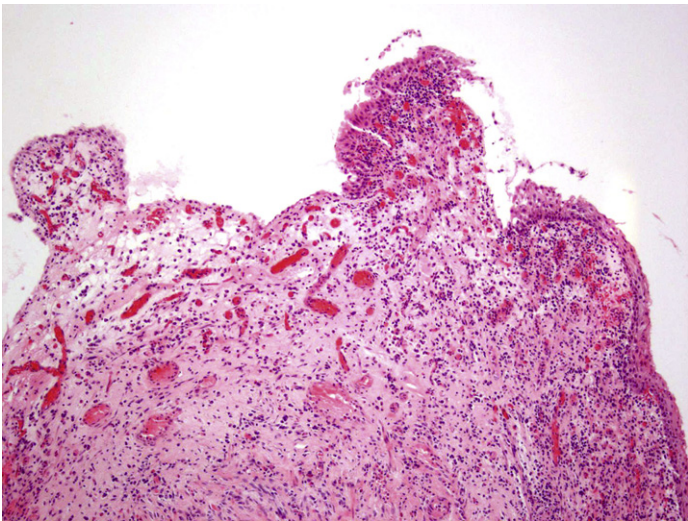


Fig. 7. Polypoid cystitis (hematoxylin-eosin, original magnification $\times 4$).

and a single prominent nucleolus. Each of the 41 cases lacked definitive hyperchromasia and nuclear pleomorphism, which are key criteria in differentiating benign, reactive lesions from neoplasia.

Polyomavirus

BK and JC are double-stranded DNA viruses of the papovavirus family that can induce cytologic changes concerning for dysplasia.¹⁵ These viruses live latently in the epithelium of the urinary tract and are asymptomatic. Use of systemic chemotherapeutic agents, primarily cyclophosphamide, as well as other clinical scenarios of immunodeficiency can lead to reactivation of

these latent human polyoma viruses.¹⁶ Atypical cellular features are usually first identified on urine cytology sampling where nuclear inclusions and/or chromatin irregularities are noted. Polyomavirus cellular changes often do not appear on histologic examination of biopsy specimens due to the virus' preference to infect the superficial cell layer, which can be lost in processing.¹⁵ Efforts to use analysis of DNA content to differentiate virally infected cells from true neoplastic cells have historically been unsuccessful due to aneuploidy.¹⁷ Correlation with clinical history, knowledge of patient immune status, and familiarity with common nuclear changes associated with reactivated viral infections are all crucial to avoid overdiagnosis of malignancy in this patient population.¹⁶

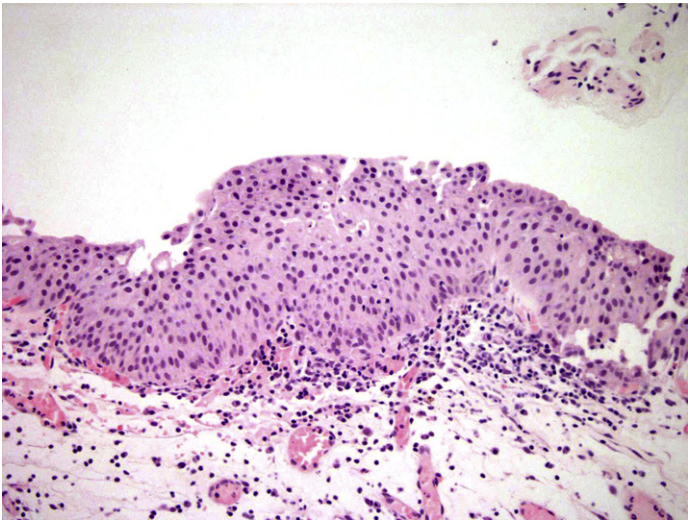


Fig. 8. Flat urothelial hyperplasia recognized as thickened urothelium with no atypia (hematoxylin-eosin, original magnification $\times 20$).

HYPERPLASIA AS A CONTRIBUTOR TO A DIAGNOSIS OF ATYPIA/DYSPLASIA

The 2 most common types of hyperplasia identified in the urinary bladder are simple (flat) and papillary. Flat hyperplasia is defined as thickened, but cytologically normal, urothelium, usually greater than 7 cell layers in thickness (see Fig. 8).¹ Flat hyperplasia has occasionally been associated with the presence of mild atypia, but an evaluating pathologist should have a low threshold for addressing this in the diagnosis. Difficulty in definitively determining the presence of flat hyperplasia may be secondary to tangential sectioning of the tissue during processing.⁶ Flat urothelial hyperplasia usually occurs in the clinical setting of inflammation or lithiasis (bladder stones) but has also been identified adjacent to papillary-type neoplasms.⁹

Papillary urothelial hyperplasia appears histologically as undulating epithelial thickening devoid of significant cellular atypia (Fig. 9). These papillary fronds may contain small, dilated vessels that appear as rudimentary vascular cores but lack the branching or more complex architecture that place this into a papillary neoplastic category.¹⁸ Similar to flat hyperplasia, mild cytologic changes in the background of inflammation and instrumentation are permitted. Any indication that the atypical features are disproportional, given the clinical setting, should guide pathologists to consider a preneoplastic process and thus a diagnosis of papillary hyperplasia with dysplasia.¹⁹ Taylor and colleagues¹⁸ examined 16 cases of papillary hyperplasia and were unable to definitively determine if papillary hyperplasia, with no evidence of atypia, would progress to neoplasia without intervention. Furthermore, the investigators postulated

that diagnosing papillary hyperplasia in a patient with a history of urothelial neoplasia likely represented a recurrence. Conversely, papillary hyperplasia with atypical features, dysplasia, or focal CIS may predispose patients to increased risk for disease progression.¹⁹

METAPLASTIC PROCESSES AND THEIR RELATIONSHIP TO BLADDER ATYPIA AND NEOPLASIA

Metaplasia is defined as a change (often reversible) from one differentiated cell type to another.²⁰ In cases of the urothelium, metaplasia often occurs in the setting of an inflammatory process or after instrumentation. Although metaplasia, by definition, is not a neoplastic process, atypia in these metaplastic cells can raise concern for less common malignancies of the bladder, such as adenocarcinoma or squamous cell carcinoma.

Squamous Metaplasia

Squamous metaplasia of the bladder involves replacement of urothelium by squamous epithelium and may be either nonkeratinizing or keratinizing. In some instances, nonkeratinizing squamous metaplasia is normal, such as in the trigone of the bladder in women.²¹ Chronic inflammatory processes, often seen in patients with spinal cord injury or persistent in-dwelling catheters, may increase the likelihood of developing squamous metaplasia, which can present as leukoplakia on cystoscopy. Although keratinizing squamous metaplasia is traditionally associated with cystitis, bladder stones, and schistosomiasis, it may also be associated with concurrent or subsequent

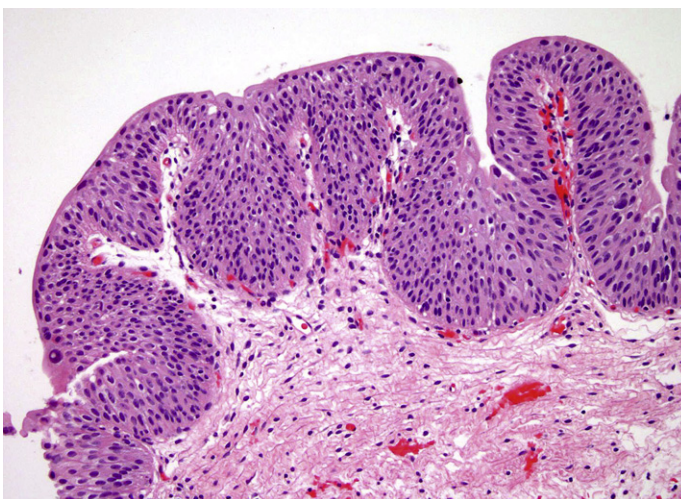


Fig. 9. Papillary hyperplasia shows upward tenting of vessels, suggesting a possible early papillary lesion in some instances (hematoxylin-eosin, original magnification $\times 20$).

malignancy and thus should be regarded with higher suspicion and additional clinical follow-up (**Fig. 10**).²²

Cystitis Cystica et Glandularis

Cystitis cystica et glandularis (CCEG) is a benign process defined as cystic changes within von Brunn nests (cystitis cystica) that develop metaplastic changes of the cellular lining to columnar or cuboidal epithelium (**Fig. 11**).²³ Similar to other metaplastic processes, CCEG is attributed to chronic inflammation/irritation and favors but is not restricted to the trigone of the bladder. CCEG is further subdivided into usual and intestinal types, although in practice this subcategorization is often not frequently used.

Intestinal Metaplasia

Intestinal metaplasia (IM) is a proliferation of epithelium in the urinary bladder characterized by gland-like structures lined with mucin-secreting cells (**Fig. 12**).²⁴ These mucin-secreting cells resemble goblet cells, which are found in the colonic mucosa of the lower gastrointestinal tract.²³ In a study by Corica and colleagues,²⁴ 53 cases of IM in the bladder were evaluated with long-term follow-up (mean >12 years among the 2 case groups²⁴). The investigators determined that the presence of IM was not a strong risk factor for the development of overt malignancy. Smith and colleagues²³ evaluated 19 cases of IM and found no evidence carcinoma at follow-up (mean 4.4 years²³). Additionally, although 37% of the cases with IM had co-existing carcinoma, the investigators believed that the association between the 2 processes did

not imply that IM was the precursor lesion. One study has suggested that pure adenocarcinomas of the urinary bladder (as opposed to urothelial carcinoma with glandular differentiation) are derived from IM, but attempts to definitively associate IM as premalignant have yet to be proven.²⁵ Extensive IM has been suggested to predispose patients to a greater risk for developing adenocarcinoma, but this frequently cited association is based on a single study²⁶ and no additional evidence has been identified in the current literature.

Glandular Metaplasia with Dysplasia

Glandular metaplasia (sometimes used interchangeably with IM²⁴) has been associated with cytologic atypia in rare cases and can be further divided into glandular metaplasia with low-grade/high-grade dysplasia.²⁷ Low-grade dysplasia shares morphologic features with tubular adenomas of the colon, including columnar nuclei that maintain polarity and uniformity. In contrast, adenocarcinoma in situ (glandular metaplasia with high-grade dysplasia) demonstrates overt atypia, including nuclear stratification, atypical mitoses, and nuclear pleomorphism (**Fig. 13**).²⁸

Villous adenomas of the urinary tract (also referred to as glandular metaplasia with an exophytic growth pattern⁸) histologically appear identical to colonic villous adenomas and consist of pseudostratified columnar mucosa with mucin-secreting cells and epithelial projections of variable size. Villous adenomas in the bladder have been associated with invasive adenocarcinoma, squamous cell carcinoma, and urothelial CIS.²⁹ These lesions are exceedingly rare but, when identified without concurrent carcinoma, seem to have

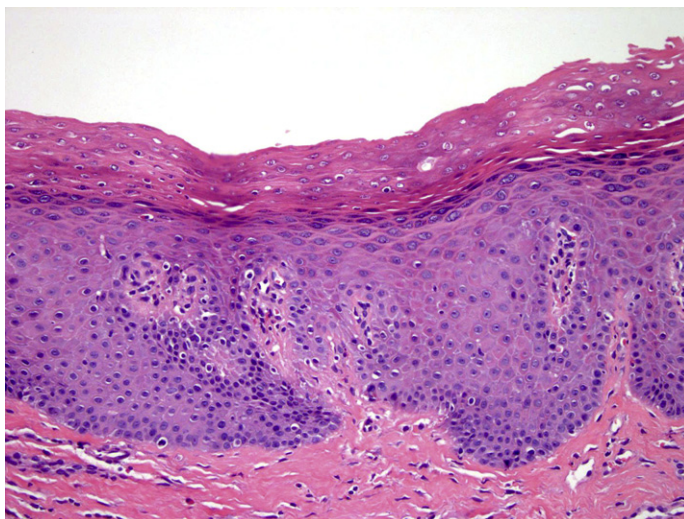


Fig. 10. Keratinizing squamous metaplasia (hematoxylin-eosin, original magnification $\times 20$).

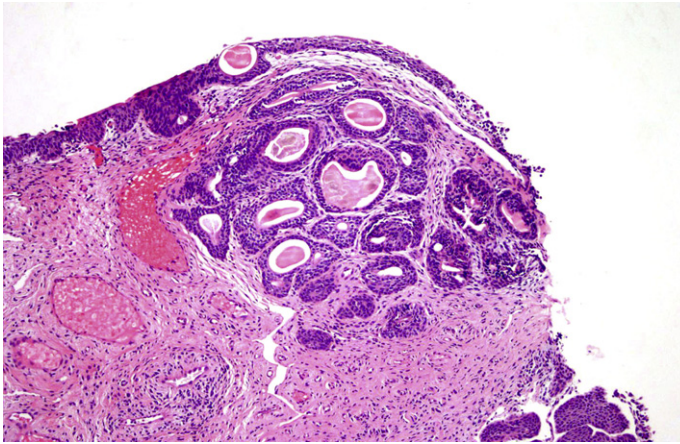


Fig. 11. CCEG (hematoxylin-eosin, original magnification $\times 10$).

an excellent prognosis for patients.³⁰ As with villous adenomas of the colon, extensive sampling is imperative to definitively rule out stromal invasion or focal adenocarcinoma in situ.⁸

TREATMENT EFFECT AS A CAUSE OF ATYPIA AND DYSPLASIA

Nonsurgical intervention for bladder and/or prostate neoplasia involves a variety of treatments, including systemic chemotherapy, intravesicular therapy, and radiotherapy. Each treatment modality poses its own challenge to pathologists secondary to the inflammation and atypia associated with each intervention. Accurate determination of the cytologic and morphologic changes secondary to treatment effect requires a detailed understanding of what effects should be expected with individual therapies. Although several

therapies may induce many reactive changes that may be interpreted as atypia, some—like radiation cystitis—may be a risk factor for the development of bladder neoplasia as well.

Radiation Therapy

Approximately one-fourth of all patients with muscle invasive bladder carcinoma undergo some form of radiotherapy.³¹ In addition, many patients diagnosed with prostate cancer also undergo various forms of radiation therapy that can ultimately affect the bladder lining based on its proximity. On cystoscopy, edema, ulceration, and erythema are common findings in addition to areas of mucosal hemorrhage. Histologically, the urothelium shows radiation atypia, which includes cellular enlargement, multinucleation, vacuolization, and chromatin clearing (**Fig. 14**).³¹ In addition to

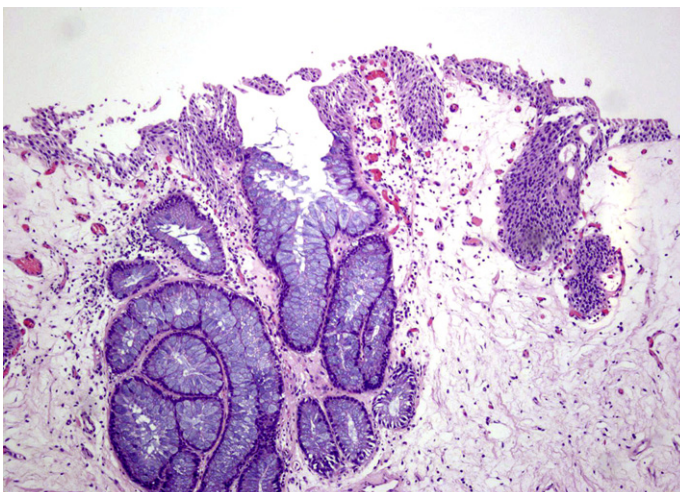


Fig. 12. IM showing mucin-containing goblet cells (hematoxylin-eosin, original magnification $\times 10$).

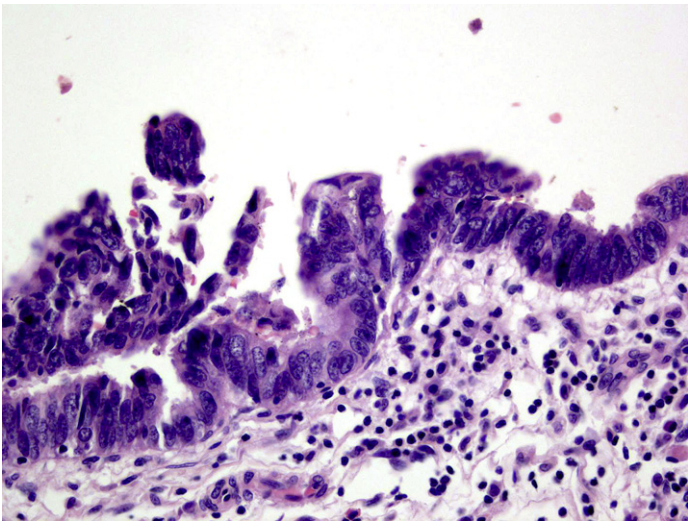


Fig. 13. Adenocarcinoma in situ (glandular metaplasia with high-grade dysplasia) shows overt neoplastic alterations (hematoxylin-eosin, original magnification $\times 40$).

inflammation and cytologic atypia identified in the epithelium, vascular changes secondary to the radiation include edema, vascular proliferation, vessel wall hyalinization, and thrombosis. Ischemic changes caused by exposure to radiation can lead to long-term sequelae, such as mucosal denudation, contractures, and fistula formation.³²

Chemotherapy

Chemotherapeutic regimens in the treatment of bladder cancer consist of intravesical and/or systemic agents, many of which can incite atypia of the urothelium. Two of the most common intravesical agents are triethylenethiophosphoramide

(thiotepa) and mitomycin C. Thiotepa (an alkylating agent) and mitomycin C (an antibiotic with anti-tumor properties) both produce similar cytologic and architectural changes to the urothelium, including denudation and atypia of the umbrella cells with features of increased size, multinucleation, and vacuolization.³¹ Additional forms of cellular atypia that occur following treatment with these 2 agents include degenerative changes and membrane alterations that may incite a diagnosis of atypia. Other intravesicular topical agents, such as doxorubicin and epirubicin, have been implicated in causing cystitis and similar cytologic changes, but details of these changes have not been studied thoroughly.³¹

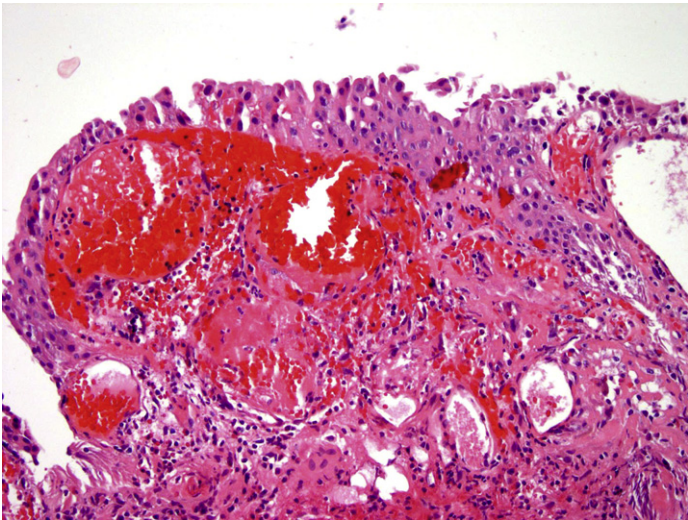


Fig. 14. Radiation atypia with a background of inflammation, nuclear atypia and edema (hematoxylin-eosin, original magnification $\times 20$).

In addition to intravesicular chemotherapy with the oxazaphosphorine class of alkylating agents, systemic chemotherapy with cyclophosphamide has been identified as a cause of bladder urothelial atypia.^{33,34} Often used in the therapy of autoimmune conditions, such as systemic lupus erythematosus and rheumatoid arthritis, and lymphoproliferative disorders, this alkylating agent undergoes metabolism to produce acrolein and phosphoramidate mustard, which are excreted in the urine and are exposed to the superficial bladder mucosa.³⁵ Clinically, patients can present with urinary symptoms and hematuria, which may prompt clinicians for cystoscopic evaluation and biopsy. Grossly, the mucosal surface can appear erythematous, edematous, and possibly hemorrhagic. Microscopically, large multinucleated cells are seen, caused by the arrest of cell division secondary to exposure to the active metabolites of cyclophosphamide. Nuclei are variably enlarged with irregular membranes, coarse chromatin, and irregularly sized and shaped nucleoli.³¹ These effects are similar to changes induced by radiation therapy. Cyclophosphamide has also been associated with hemorrhagic cystitis.³⁶

From a pathologist's perspective, one of the greatest difficulties in the setting of chemotherapeutic treatment is determining whether atypia is the result of therapy or whether the atypia represents early neoplastic changes secondary to new or recurrent disease. Several studies have determined that cyclophosphamide therapy is associated with an up to 9-fold increase in the development of bladder carcinoma.³⁷ Furthermore, chemotherapeutic agents have been associated with benign epithelial proliferations, which can mimic invasive carcinoma due to an infiltrative growth pattern into the lamina propria of the bladder mucosa.³⁸ These pseudocarcinomatous proliferations cause several challenges for pathologists due to the elevated risk for developing cancer in patients treated with chemotherapy and the limited sampling on biopsy.³⁸

Bacillus Calmette-Guérin Therapy

Bacillus Calmette-Guérin (BCG) therapy is the most common intravesicular immunotherapy agent used worldwide for the treatment of superficial and noninvasive high-grade bladder neoplasia.³⁹ BCG is a pleiotropic immune stimulator that can limit tumor progression by recruitment of an antitumoral immune response.²⁸ Microscopically, BCG therapy most notably causes acute and chronic inflammation associated with noncaseating granulomas but may also induce

mucosal ulceration, denudation, and reactive urothelial atypia.⁴⁰

Photodynamic Therapy

Photodynamic therapy is a newer, less common modality used in treatment of bladder neoplasia.⁴¹ Photodynamic treatment is administered either systemically or intravesicularly, subsequently inducing necrosis of tumor cells when exposed to a light source.⁴² In addition to inducing coagulative necrosis and hemorrhage, adjacent benign mucosa may be affected by the treatment. Cytologic atypia is not traditionally associated with this therapy and should raise suspicion if identified on microscopy examination.²⁸

Ketamine Cystitis

An exceedingly rare, but notable, mimicker of CIS is ketamine cystitis, which can occur in the setting of chronic exposure to this drug. These patients typically report clinical symptoms of dysuria, urgency, hematuria, and incontinence. On cystoscopy, a small capacity, erythematous bladder is seen. Microscopically, ulceration and acute inflammation are the most common findings. A 2009 study from Oxley and colleagues⁴³ looked at 17 patients with reported ketamine cystitis, 10 of which were described as having significant urothelial atypia on histologic examination concerning for CIS. The investigators reported that despite nuclear enlargement and disorganization of cells seen on biopsy, the changes identified were likely reactive and did not represent a preneoplastic process.

IMMUNOHISTOCHEMISTRY AS AN ANCILLARY TOOL

Although extensively studied, the use of IHC in the diagnosis of urothelial neoplasia has remained somewhat challenging. As discussed previously, discerning reactive atypia from dysplasia and CIS remains one of the greatest topics of contention in urologic pathology. Several studies have examined the utility of IHC in noninvasive lesions of urothelium, in particular atypia and CIS, to determine what role, if any, they may serve in reaching the appropriate diagnosis.

Several studies have been done to determine which IHC markers could be useful to pathologists to differentiate reactive atypia from dysplasia. In 2001, 1 study evaluated 25 cases of non-neoplastic urothelium (15 cases of reactive atypia and 10 cases of normal urothelium) using 3 common IHC stains: cytokeratin 20, CD44, and p53.⁴⁴ Cytokeratin 20 stains cytoskeletal intermediate filaments found in gastrointestinal mucosa,

urothelium, and Merkel cells and is generally restricted to the umbrella cell layer in normal urothelium. p53 is a tumor suppressor gene implicated in many malignancies, including bladder carcinoma⁴⁵; under normal conditions, p53 demonstrates a weak cytoplasmic signal in the urothelium. Finally, CD44 is an immunomarker previously studied as a possible prognostic factor in papillary urothelial neoplasms and has been found under normal conditions to reside in the basal layers of the urothelium.⁴⁵ A combinatorial approach has been used with these 3 IHC markers to aid in the distinction between normal urothelium with atypia and CIS. Specifically, intense nuclear p53 expression (that correlates with p53 mutation) coupled with full-thickness CK20 expression and loss of CD44 favors CIS.^{44,46} Although this overall finding in larger studies seems promising, use of these markers routinely on individual cases can often be problematic, with variability in intensity and distribution of markers common.

SUMMARY

Evaluation of the bladder urothelium is a diagnostically challenging process that involves not only subtleties in morphologic evaluation but also an awareness of patient history to elucidate sources of atypia unrelated to neoplastic transformation. Common challenges in distinguishing the categories of reactive atypia from atypia of uncertain significance and dysplasia include the presence of inflammation, therapy, and prior instrumentation. Despite improved investigation into the utility of IHC markers, microscopic assessment remains the definitive approach to achieving the most accurate urothelial diagnosis possible.

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Restaging Transurethral Resection for Non-Muscle Invasive Bladder Cancer

Who, Why, When, and How?

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KEYWORDS

- Non-muscle invasive bladder cancer • Transurethral resection • Repeat resection
- Second-look cystoscopy • Restaging • Upstaging • Understaging

KEY POINTS

- Understaging rates of up to 40% for non-muscle invasive bladder cancer have been reported based on radical cystectomy data.
- Absence of muscularis propria MP in the specimen leads to a significantly higher rate of understaging (60%–78%).
- Patients with high-grade (HG) Ta and HG T1 tumors, regardless of presence of muscle, are strongly encouraged to undergo a restaging transurethral resection (TUR).
- Repeat resection should be performed 2 to 6 weeks following initial TUR.
- Deep biopsies in the base and periphery of the old resection site should be performed.

Non-muscle invasive bladder cancer (NMIBC) comprised the vast majority of the estimated 73,510 new cases of bladder cancer diagnosed in the United States in 2012.¹ Approximately 70% to 75% of patients with bladder cancer initially present at a low stage (stage 1), a category that includes carcinoma in situ (Tis – 1–10% alone as primary), tumors confined to the urothelial mucosa (Ta – 70%–80%), and those that invade only the underlying lamina propria (T1 – 20%).^{2–4} The prognosis for patients with NMIBC is generally good, with approximately 80% to 90% of patients alive at 5 years.² In contrast, muscle-invasive bladder cancer, which represents about 25% of cases, has a significantly lower relative 5-year survival rate of 17% to 66% depending on tumor stage.^{2,5} Epidemiologic evidence demonstrates

that these trends in incidence and survival for noninvasive and invasive bladder cancer have remained relatively stable since 1993.² The most significant risk factor for bladder cancer is cigarette smoking.⁶ While the risk may decrease with smoking cessation, former smokers still have a higher risk of bladder cancer than never smokers.⁶ Additionally, in patients with NMIBC, current tobacco use and cumulative lifetime exposure are closely associated with recurrence and progression.^{7,8} There is no currently accepted genetic or inheritable cause of urothelial carcinoma of the bladder, but studies suggest that polymorphisms in 2 carcinogen-detoxifying genes, GSTM-1 and NAT-2, may be responsible for increased susceptibility to developing bladder cancer in certain patients.⁹

Disclosures: None.

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WHO TO RESTAGE

Understanding the Predictors of Understaging, Recurrence, and Progression

Patients with NMIBC represent a heterogeneous group and demonstrate a broad range of outcomes with respect to recurrence, progression, and survival. Accurate staging and a fundamental understanding of the pathologic findings that predict outcome are therefore of utmost importance in clinical management. Thus, when considering the value of restaging transurethral resection (TUR), the first question that must be addressed is “who?” That is, which patients may benefit from additional resection rather than proceeding to intravesical chemotherapy/surveillance cystoscopy? Importantly, restaging TUR, which assumes a complete initial TUR, is distinguished here from a repeat resection performed when a complete initial TUR cannot be accomplished.¹⁰

Most (55%–75%) of Ta tumors are low grade (LG), and patients with high-grade (HG) tumors are at much greater risk of recurrence, progression, and death from bladder cancer compared with those with LG disease.^{2,11,12} Long term follow-up of Ta LG tumors demonstrates that the overall recurrence rate is 55%, with 6% and 20% experiencing progression of stage and/or grade, respectively.¹³ In contrast, 30% to 35% of Ta HG tumors will progress to at least T1 disease.^{11,12} Ta HG urothelial cancer is associated with a significant risk of progression and death as manifested by progression-free survival and disease-specific survival rates of 61% and 74%, respectively, according to 1 study.¹⁴ This has important implications when considering the merits of restaging TUR, since adequate tumor stage and grade information clearly guides future management decisions, including administration of intravesical therapy or a recommendation for early cystectomy in patients found to be understaged at initial TUR.

Along with Ta HG bladder cancer, carcinoma in situ (CIS) and T1 cancers are all considered high-risk NMIBC. Clinical stage T1 tumors, those invading beyond the mucosa but confined to the lamina propria at the time of TUR or biopsy, represent approximately 20% of NMIBC and behave more aggressively than Ta tumors. They may also be classified as HG or LG, but in contrast to stage Ta, most T1 tumors are HG and therefore have a high risk of progression.^{12,15} Within stage T1 urothelial cancer, studies have shown that deeper invasion into the lamina propria leads to higher progression rates (58%) compared with superficial invasion (36%), and depth of invasion (as measured by muscularis mucosae involvement) is a significant independent predictor of

progression.^{15–17} While this is likely related in part to increased aggressiveness of more deeply invading tumors, this may also be indicative of the increased likelihood of an incomplete endoscopic resection in patients with tumors invading into the muscularis mucosae. Thus, adequate TUR is critical not only to ensure accurate staging and guide future management options, but also to remove all tumor from the bladder.

It should be emphasized that invasion of the muscularis mucosae is still considered non-muscle invasive disease in contrast to muscularis propria (MP) invasion, which is the hallmark of true muscle invasion (stage T2). Therefore, a TUR specimen with only muscularis mucosae and no MP is still considered inadequate for determination of muscle invasion. **Fig. 1** demonstrates a cT1 tumor with MP present in the specimen and not involved by cancer. **Fig. 2** demonstrates a cT1 tumor with only muscularis mucosae present in the specimen; it is therefore inadequate for the determination of muscle invasion due to lack of MP. The ability to distinguish between the MP and muscularis mucosae is challenging, however, as these images show. MP is a distinct layer of muscle fibers, whereas muscularis mucosae is typically a few smooth muscle cells arranged in fibers dispersed throughout the lamina propria.¹⁸

Sylvester and colleagues¹⁹ reviewed 7 European Organisation for the Research and Treatment of Cancer (EORTC) trials in NMIBC and found that the probability of progression for T1HG disease ranged from 20% to 48% at 5 years, and the

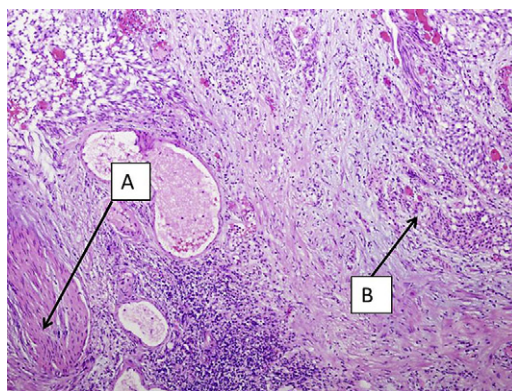


Fig. 1. TUR specimen demonstrating muscularis propria present in the specimen but not involved by urothelial carcinoma. Image shows a thick bundle of muscle fibers (A) that are seen in the resected specimen and are separate from the area of tumor (B). The tumor is high grade, demonstrating significant cytologic atypia with a desmoplastic reaction and lamina propria invasion (stage T1). (Courtesy of Lan Gellert MD, PhD, Department of Pathology, Vanderbilt University.)

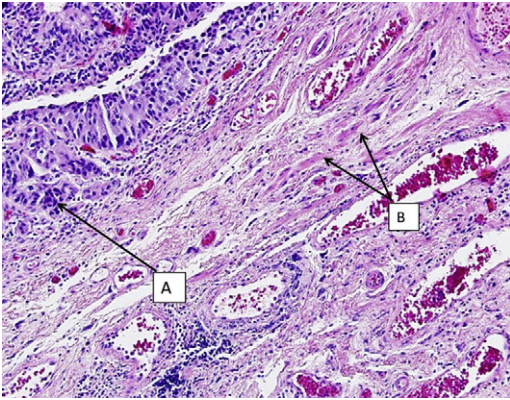


Fig. 2. TUR specimen demonstrating muscularis mucosae present in the specimen but no evidence of muscularis propria. Image shows an HG urothelial carcinoma with invasion of the lamina propria (A). There are scant fibers of smooth muscle cells that represent the muscularis mucosae (B) present in the lamina propria, but there is no evidence of distinct thick muscle bundles as would be seen if muscularis propria were present in the specimen. (Courtesy of Lan Gellert MD, PhD, Department of Pathology, Vanderbilt University.)

most important predictive factor was the presence of concomitant CIS. Patients who had T1 HG urothelial cancer without CIS had a 29% probability of progression at 5 years, whereas those with concomitant CIS had a 74% probability of progression at 5 years.¹⁹ Similarly, in a multivariate analysis of predictors of recurrence, progression, and survival in primary Ta and T1 urothelial cancer, Millan-Rodriguez and colleagues²⁰ demonstrated that patients with CIS had almost twice the risk of recurrence and progression and 3 times the risk of mortality than those without CIS. CIS as a stand-alone entity is rare and represents only 1% to 10% of NMIBC. Additionally, although it is a noninvasive lesion, its presence is considered a strong indicator of risk for progression and HG disease.^{3,4,21} Patients with CIS in the primary TUR specimen in combination with Ta or T1 tumors should therefore be strongly considered to undergo restaging TUR for accurate staging and prognosis as they can potentially harbor more aggressive disease.

To better understand which patients require restaging TUR, factors besides grade, stage, and CIS need to be considered. Several studies have found that the number of prior recurrences, multiple tumors, large tumor size (>3 cm), and the presence of hydronephrosis are all predictors of recurrence and progression and are additional indicators of high-risk disease.^{19,20,22} In particular, tumor size and hydronephrosis are associated with muscle invasion and therefore often indicate tumor

understaging in patients thought to have non-muscle invasive disease.²² Additional pathologic findings that are concerning for progression and high-risk of disease-specific mortality are micropapillary variants of urothelial carcinoma and lymphovascular invasion (LVI).^{23,24} The group at MD Anderson Cancer Center reviewed its experience with the micropapillary variant of urothelial carcinoma and found that in those who underwent intravesical bacillus calmette-guerin (BCG) therapy (all T1), only 19% (5/27) of patients were disease-free at a median follow-up of 30 months.²³ Early cystectomy is typically strongly considered in these patients, and restaging TUR is imperative if a bladder preservation strategy is employed, in light of the high risk of progression. With respect to LVI, Cho and colleagues²⁴ demonstrated that it was an independent predictor of recurrence and progression in 118 patients with NMIBC. Similarly, Resnick and colleagues demonstrated that patients with LVI at TUR were more likely to experience upstaging at the time of radical cystectomy.²⁵ Finally, there may eventually be a role for molecular profiling to better define the need for restaging TUR. Known markers of disease progression include p53, p16, fibroblast growth factor 3 (FGFR3), E-cadherin, and urokinase-plasminogen activator.^{26–28} Future research may help to determine whether these markers can predict which patients may have occult invasive disease and more accurately stratify for risk patients with NMIBC after initial TUR.

In summary, given the data on upstaging, recurrence, and progression in patients with high-risk NMIBC, restaging TUR is indicated in any patient found to have high-grade and/or T1 disease but no MP in the specimen, unless radical cystectomy is planned. Both the 2007 American Urological Association (AUA) guidelines and the 2011 European Association of Urology (EAU) guidelines for the management of NMIBC unequivocally recommend restaging TUR in this setting.^{29,30} The clinical relevance of this is apparent in light of contemporary reports revealing only 47% of patients with muscle present in the specimen on initial TUR.³¹ Whether restaging TUR is necessary in high-risk patients despite the presence of MP in the initial TUR specimen has historically been an area of debate. However, as will be discussed further, there is a substantial risk of upstaging even when MP is present in the initial TUR specimen, and therefore restaging TUR is increasingly considered standard of care in any patient with HG and/or T1 disease planning on proceeding with a bladder-sparing approach. According to the EAU guidelines, a second restaging TUR is recommended in any patient with HG and/or T1

bladder cancer on initial TUR, regardless of the presence of MP in the specimen (level of evidence 2a).^{30,32} The AUA guidelines also suggest that it is appropriate to consider restaging TUR in patients with HG T1 with MP and also HG Ta patients in an effort to improve the accuracy of clinical staging, although there is no explicit recommendation in favor of restaging TUR in these patients.²⁹

WHY TO RESTAGE
Evidence for Understaging at Initial TUR

A central rationale for restaging TUR in high-risk NMIBC is the concern over clinical understaging given the specter of missing occult muscle-invasive disease. Available data from patients undergoing radical cystectomy for NMIBC suggests that there is a significant rate of clinical understaging. In an analysis of 78 patients who had radical cystectomy for non-muscle invasive disease Dutta and colleagues³³ demonstrated that 31 cases (40%) were clinically understaged, and most of these (80%) were cT1 based on their initial TUR. Of the 63 overall cT1 patients in the cohort, 26 (41%) had no MP in the specimen, and 16 (62%) of those without muscle were understaged compared with only 11 of 37 (30%) cT1 patients understaged with MP present and uninvolved.³³ These findings illustrate 2 salient points in TUR for NMIBC. First, the absence of MP at the time of pathologic analysis leads to a significant rate of understaging, and second, the rate of clinical understaging is as high as 30%, even with muscle in the specimen. Other contemporary studies have demonstrated similar rates of understaging.^{34–36} In a series of 95 patients from the University of Michigan undergoing radical cystectomy for cT1 bladder cancer, 26 (27%) patients were understaged by TUR.³⁴ Bianco and colleagues reported an identical rate of 27% understaging for 66 cT1 patients following radical cystectomy.³⁵ **Table 1** illustrates the findings of several series comparing rates of clinical understaging based on review of radical cystectomy specimen. Thus, restaging TUR was first advocated in the setting of T1 disease without MP in the resection specimen in an effort to avoid the high rates of understaging found across these studies.

Risk factors for understaging relate primarily to the thoroughness of the TUR, with the main goal of any resection being to completely excise all tumor tissue with negative margins and obtain MP in the specimen for pathologic analysis. Absence of MP is an important indicator of a potentially incomplete resection.³⁷ A contemporary analysis by Badalato and colleagues³⁸ found that

Table 1 Rates of understaging in NMIBC based on radical cystectomy specimen		
Study, Year	Number of Patients	Understaging (%)
Dutta et al, ³³ 2001	78	30% (MP) 62% (no MP)
Badalato et al, ³⁸ 2011	114	50% (MP) 78% (no MP)
Weizer et al, ⁶³ 2009	95	27%
Gupta et al, ³⁶ 2008	167	50%
Bianco et al, ³⁵ 2004	66	27%
Fritsche et al, ⁴⁰ 2010	1136	51%
Ficcara et al, ⁶⁴ 2005	70	43%

up to 78% of cT1 patients without MP in the specimen were upstaged at the time of cystectomy. However, as mentioned, understaging may occur even in the presence of muscle up to 30% of the time.³³ Muscularis mucosae involvement, mixed histology, and urethral involvement (in particular tumor in the prostatic urethra) are all additional predictors of understaging at initial TUR.^{34,39} Demographic features that may independently predict understaging include female gender and age; however these may simply represent surrogate markers of a less aggressive TUR.^{38,40}

Impact of Restaging TUR on Risk of Understaging

Several series have demonstrated significant improvement in the diagnostic accuracy of clinical staging following a restaging TUR. In a study of 150 patients undergoing a second TUR, Herr demonstrated that 24% of Ta cases (n = 38) were upstaged to T1 and 8% to T2. Similarly, 28% of all T1 tumors (n = 58) were upstaged to T2, and in T1 patients with no MP (n = 23) on primary TUR, 49% were upstaged to T2.⁴¹ For all NMIBC patients (n = 96), the cT0 rate on restaging TUR was only 25%, and upstaging was present in 29% of cases.⁴¹ Schwaibold and colleagues⁴² reported similar findings following their experience in 136 patients who underwent restaging TUR, with 21% demonstrating an increase in T stage and 52% with residual tumor. Of those with residual tumor, 86% of disease was located in the prior resection site. However, other series, such as that reported by Schips and colleagues,⁴³ have reported lower rates of upstaging and residual disease. In this cohort of 110 patients, 40 (36%)

had residual disease. Of these, 22 (55%) patients were correctly staged; 9 (8%) patients were down-staged, and another 9 (8%) patients were up-staged following restaging TUR.⁴³ When broken down by stage, both cTa and cT1 tumors had similar rates of upstaging at 6.4% and 7.9%, respectively.⁴³ In another group of NMIBC patients (n = 710), Herr and colleagues found that 61% had residual disease on restaging TUR.⁴⁴ Importantly, restaging TUR pathology (T0 vs Tany) was a significant independent predictor of any tumor recurrence (HR 1.3) and stage progression (hazard ratio [HR] 6.9, $P < .001$ for both). They also found that none of the patients with LG NMIBC were up-staged on restaging TUR, supporting the general consensus that Ta LG tumors do not require restaging transurethral resection of bladder tumor (TURBT).⁴⁴

The reported variation in these rates of upstaging is likely due to a combination of factors, including both TUR technique and pathologic interpretation.^{18,45} Several studies have demonstrated that more experienced surgeons are more likely to obtain MP at TUR, and surgeon experience may impact the likelihood of recurrence following TUR.^{37,46} However, in 1 cohort focusing on 523 patients with cT1 NMIBC seen at Memorial Sloan-Kettering Cancer Center (MSKCC) and undergoing restaging TUR either at MSKCC or elsewhere, a similar proportion of patients (21% MSKCC, 18% outside) were upstaged to T2 regardless of the institution where restaging TUR was performed.³¹ This observation suggests that even in experienced hands, repeat TUR is necessary in patients with high-risk NMIBC. Additionally, 84 patients with NMIBC at restaging TUR went on to receive immediate cystectomy following repeated resection, and 19 (23%) were upstaged to pT2 or higher, demonstrating that even though a restaging TUR may improve the diagnostic accuracy, there is still a substantial risk of understaging.³¹ **Table 2** summarizes and compares the rates of upstaging and residual disease reported in several contemporary series of NMIBC patients following restaging TUR. Data from these centers of excellence cumulatively support the fact that even in the best of hands, regardless of how thorough a resection for high-grade T1 disease, a repeat TUR should be performed to ensure accurate staging and for removal of any remaining residual noninvasive disease.

Impact of Restaging TUR on Response to Intravesical Therapy

Favorable response rates following intravesical therapy after a second TUR have been

Table 2
Rates of upstaging and residual disease after repeat TUR

Study, Year	Number of Patients	Upstaging	Residual Tumor
Herr, ⁴¹ 1999	96	29%	75%
Schwaibold et al, ⁴² 2006	136	21%	52%
Schips et al, ⁴³ 2002	110	8%	18%
Dalbagni et al, ³¹ 2009	523	20%	–
Divrik et al, ¹⁰ 2010	105	7%	33%

demonstrated in multiple studies when compared with a treatment following a single TUR. In a study from MSKCC comparing 215 patients who underwent restaging TUR followed by 6-week induction intravesical BCG with 132 who underwent a single TUR then received BCG therapy, the recurrence rate at 1 year and progression rate at 3 years were 17% and 7%, respectively for those who had a second TUR compared with 61% and 34% for those who had no restaging.⁴⁷ The rate of tumor presence at first cystoscopy after intravesical therapy was almost twice as high in those who were not restaged (57%) compared with those who had a second TUR (29%). On multivariate analysis, restaging TUR before intravesical BCG was a significant independent predictor of lower rates of recurrence and progression.⁴⁷ In a contemporary analysis of patients undergoing a repeat TUR followed by induction and maintenance BCG, those who were confirmed to have no residual tumor had improved response rates, with only 11% experiencing recurrence during follow-up (2.7 years) compared with 28% of those who had tumor present at second TUR.⁴⁸ Data from a prospective, randomized clinical trial of mitomycin C (MMC) following TUR also support the findings of improved response rates for those undergoing repeat resection. One hundred forty-two patients were randomized to either single versus restaging TUR (at 2–6 weeks) followed by a perioperative (within 24 hours – mean 2 hours) dose of intravesical MMC and then weekly instillations for 7 more weeks.⁴⁹ Recurrence-free survival (RFS) was significantly better for patients undergoing restaging TUR (74%) compared with a single TUR (37%). The median RFS was 27 months for the restaging TUR group versus 12 months for the single TUR group. However, there was no significant difference in progression during the follow-up period (mean

follow-up 31.5 months).⁴⁹ While a single perioperative dose of MMC has been well established for its role in decreasing recurrence following TUR, there is not strong evidence of an impact on disease progression, potentially explaining the similar progression rates in this study.⁵⁰ These studies support the hypothesis that restaging TUR improves the accuracy of staging, thereby appropriately allocating patients to the correct treatment groups, and for those with residual tumor, restaging TUR decreases tumor burden and appears to improve the likelihood of a complete response to subsequent therapy.^{47,51}

Impact of Restaging TUR on Cancer-Related Outcomes

As with other treatment decisions in NMIBC, the efficacy of restaging TURBT must be evaluated in terms of its effect on recurrence, progression, and survival. Evidence supporting a difference in recurrence for those undergoing restaging TUR versus single TUR has been shown by the analysis of Grimm and colleagues,⁵² who reported a 63% versus 40% 5-year RFS for repeat compared with single TUR. Similarly, other studies have reported a significant difference in 5-year RFS of 59% for patients undergoing second resection versus 32% for a single TUR.¹⁰ With respect to progression, the same group also demonstrated a significant improvement in 5-year progression free survival (PFS), with a rate of 93% for restaging TUR versus 79% for single resection.¹⁰ In addition, despite a small number of patients dying of disease (16/65, 25%), they were able to show a significantly better cancer-specific mortality for restaging TUR (5/30, 16.7%) compared with single TUR (11/35, 31.4%). On multivariate analysis, a second TUR was an independent predictor of both recurrence (HR 2.482, $P = .001$) and progression (HR 3.487, $P = .007$).¹⁰ These studies suggest that restaging TUR, in addition to providing accurate diagnostic information for better treatment allocation, may directly impact cancer-related outcomes by decreasing intravesical tumor burden.

WHEN AND HOW TO PERFORM RESTAGING TRANSURETHRAL RESECTION

Timing

Most studies suggest that restaging TUR should be performed within 2 to 6 weeks of the initial resection,^{41,53} and, in light of these data, the EAU guidelines recommend performing restaging TUR within this time window.³⁰ However, studies have reported waiting as long as 7 weeks for restaging TUR, and others have defined restaging TUR as any resection performed less than

3 months following initial resection.^{31,52} There is limited evidence to definitively support a single optimal time for repeat resection, and further investigations may help clarify this issue. Waiting for 2 weeks is likely sufficient to promote healing of the urothelium and thereby minimize the risk of perforation following sampling of previously resected areas. Delaying restaging TUR beyond 6 weeks, without a strong clinical indication, could potentially have adverse effects, including persistent hematuria from residual disease and, most importantly, disease progression due to delay of definitive treatment with intravesical therapy or radical cystectomy. It has been well demonstrated that prolonging the wait time from TUR to cystectomy increases the risk of overall mortality.⁵⁴ Particularly in light of the high rates of upstaging to muscle-invasive disease at restaging TUR, these data lend support to minimizing the lag time before second TUR to less than 6 weeks.

Technique

A restaging TUR is typically performed in the standard fashion of the initial TUR; however, particular attention is paid to deep sampling of the old resection bed.⁴⁵ The erythema and edema that occur around the time of the initial resection will have resolved, thus affording the opportunity to reassess whether a complete resection was performed at the time of the initial TUR.⁵⁵ Any evidence of residual tumor should be completely resected. A TUR loop resection should be performed of the old scar followed by a cold-cup biopsy of the base and resection edges of the old scar. It is imperative to resect detrusor muscle from the tumor bed, even if at the risk of bladder microperforation. Small asymptomatic bladder perforations are common, and do not appear to pose significant risk to the patient.⁵⁶ Each biopsy is sent in a separate container, which may potentially improve pathologic staging accuracy.⁴⁵ In addition, care should be taken to limit excess cautery, as this may lead to pathologic artifact and difficult interpretation of the specimen (**Fig. 3**). The larger sampling obtained with the TUR loop helps with a more definitive pathologic analysis, and the TUR loop can be used simultaneously to remove any residual non-muscle invasive disease. In addition to residual tumor at the site of the original resection, Brausi and colleagues demonstrated that 53% (166 of 316 patients) of patients with recurrence at the time of second TUR had tumor found at other sites. These tumors should be managed in the standard fashion and sampled separately using either cold-cup biopsy or TUR depending on size and suspicion for higher-grade disease.^{45,57}

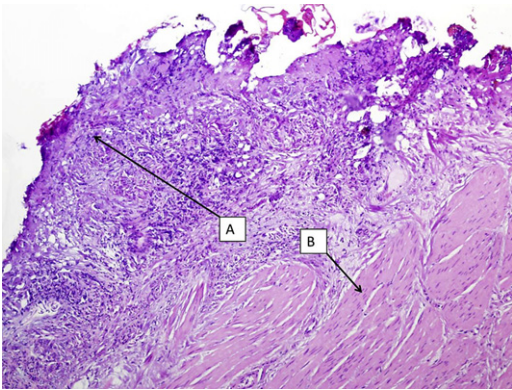


Fig. 3. TUR specimen demonstrating cautery artifact. Image shows resected tissue that is difficult to interpret due to poor cytologic detail with debris and distortion as a result of excessive cauterization (A). There are also thick muscle bundles present in the specimen (B), consistent with the presence of muscularis propria. (Courtesy of Lan Gellert MD, PhD, Department of Pathology, Vanderbilt University.)

Finally, there is increasing interest in photodynamic diagnosis (PDD) using a photosensitizer (5 aminolevulinic acid [5-ALA] or hexylaminolevulinic acid [HAL]). The dye is instilled and absorbed most rapidly by hypermetabolic or dysplastic tissue, emitting an intense red color that facilitates detection.⁵⁸ While the authors are not aware of any studies specifically addressing the use of PDD at restaging TURBT, there is strong evidence that these dyes aid in detection of tumors that would be otherwise missed by white light cystoscopy.^{59–61} Furthermore, Karaolides and colleagues recently randomized 102 patients with NMIBC to TURBT with either white light alone or with the aid of PDD.⁶² Their results suggest more successful complete tumor resection in the setting of HAL, with significant improvements in recurrence-free rates in the HAL cohort relative to the white light cohort. Whether similar results will be observed when PDD is used for restaging TUR remains to be seen, but it seems highly likely based on these data that PDD could offer both improved staging accuracy and tumor clearance in this high-risk population.

SUMMARY

The goal of restaging TUR is threefold: to improve staging accuracy, resect any residual tumor, and potentially to improve the response to intravesical treatment.^{32,49} While patients with LG Ta cancer do not require restaging TUR, a second TUR is indicated in those patients with a high risk of being understaged or harboring residual disease. This most directly applies to patients with HG

T1 disease, particularly with no MP present in the initial TUR specimen. However, patients with HG Ta are also at a significant risk of understaging and tumor recurrence, and restaging TURBT is appropriate in this population also. Other features that have been shown to increase the risk of recurrence and progression in NMIBC such as large tumors, presence of CIS, and multiple tumors may prompt restaging TUR in an effort to ensure accurate staging and improve the response rates to intravesical therapy compared with a single TUR. The second TUR should be done within 2 to 6 weeks of the initial TUR, and the base and margins of the old scar should be sampled separately for pathologic analysis. Lastly, proper patient counseling regarding prognosis is highly reliant on accurate diagnostic information and cannot be achieved without restaging TUR when clinically indicated.

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Optimal Risk-Adapted Surveillance Strategies for NMIBC, Including Upper Tract Imaging

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KEYWORDS

• Non-muscle invasive • Bladder cancer • Guidelines • Surveillance • Treatment • Imaging

KEY POINTS

- The financial burden of non-muscle invasive bladder cancer (NMIBC) continues to increase, underscoring the importance of efficient, evidence-based management of this disease. Management varies by risk (low, intermediate, or high).
- One of the treatment challenges rests in the heterogeneity within the umbrella diagnosis of NMIBC: mortality rates from low-risk disease are nonexistent, whereas those from high-risk disease approach 30% at 10 years. As such, there is concern for overtreatment of low-risk disease and undertreatment of high-risk disease.
- Following transurethral resection of bladder tumor (TURBT), consideration may be given to a single perioperative dose of intravesical chemotherapy. A European Organization for Research and Treatment of Cancer meta-analysis concluded that this practice was associated with a 12% reduction in tumor recurrence and a 39% reduction in the odds of recurrence. This finding was reportedly independent of the agent selected. An American Urological Association meta-analysis concluded there was a 17% absolute reduction in recurrence relative to TURBT alone across all risk groups. Evidence suggests, however, that the benefit of single-dose perioperative intravesical chemotherapy is limited for multiple or recurrent tumors or in cases of high-grade disease when bacillus Calmette-Guérin (BCG) therapy is planned.
- For those pursuing a bladder-sparing approach in pathologic Ta high-grade, Tis, and/or T1 disease, an induction course of intravesical BCG followed by maintenance BCG is a recommendation, with a meta-analysis suggesting a 5-year recurrence rate of 34% for those receiving TURBT and BCG maintenance.
- One of the foremost challenges to the urologist treating NMIBC is deciding when to abandon bladder-sparing therapies in favor of cystectomy. The morbidity of cystectomy is considerable, with short-term complication rates greater than 60%. However, it is also known that 40% to 50% of patients with Tis will fail BCG and nearly 25% will be pT2 or greater and 5.8% pN+ at cystectomy.

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INTRODUCTION

In 2012, there were an estimated 73 510 new cases of bladder cancer diagnosed in the United States.¹ Approximately 90% of bladder cancers are urothelial cell carcinoma (UC), with subtypes of squamous cell carcinoma and adenocarcinoma or other variants composing 5% and 2% or less of cases, respectively.² Seventy percent of newly diagnosed bladder cancer is non-muscle invasive bladder cancer (NMIBC). Although historically known as *superficial bladder cancer*, this term has been replaced by the stratification of NMIBC into 3 risk categories: low, intermediate, and high.³ Although all major guidelines agree that risk stratification of NMIBC is appropriate, there is not consensus on the definitions of each risk category (Table 1).^{4–6}

One of the treatment challenges rests in the heterogeneity within the umbrella diagnosis of NMIBC: mortality rates from low-risk disease are nonexistent, whereas those from high-risk disease approach 30% at 10 years.⁷ As such, there is concern for overtreatment of low-risk disease⁸ and under treatment of high-risk disease.⁹ Improper management of NMIBC can be costly for patients and the health care system. Bladder cancer is estimated to be the ninth most expensive cancer in the United States, with total costs of approximately \$3.98 billion in 2010, a number expected to increase to \$4.9 billion by 2020.¹⁰ It is estimated that \$39 293 of the \$65 158 average lifetime cost of treatment is associated with surveillance and management of recurrence, underscoring the importance of efficiency and quality in delivery of care for NMIBC.¹¹

Evidence-based guidelines from the American Urological Association (AUA), the European Association of Urology (EAU), and the National Comprehensive Cancer Network (NCCN) have been established to simplify the diagnosis and treatment of this heterogeneous disease. This article reviews the consensus diagnostic and treatment algorithms for NMIBC, divided into 3 risk categories, and highlights the similarities and differences in recommendations across the AUA, EAU, and NCCN guidelines. The treatments

discussed include (1) transurethral resection of bladder tumor (TURBT); (2) perioperative, postoperative, and maintenance intravesical therapy; and (3) cystectomy. When appropriate, rates of recurrence, progression, and mortality are addressed.

DIAGNOSIS, DETECTION, AND SURVEILLANCE TOOLS

This section describes the presentation of bladder cancer as well as the tools available to the urologist in its diagnosis and surveillance. Its purpose is to outline both routine and investigational tools intended to improve the management of NMIBC. Any specific recommendations regarding the use of these agents are described in subsequent sections.

The diagnosis of bladder cancer is usually preceded by hematuria. Patients with macroscopic hematuria have reported rates of bladder cancer between 13.0% and 34.5%, with microscopic hematuria associated with bladder cancer at a rate of 0.5% to 10.5%.^{12–16} New-onset irritative voiding symptoms may also indicate underlying malignancy, with or without hematuria.^{17,18}

Although cystoscopy is the mainstay of bladder cancer diagnosis and surveillance, cytology and urinary markers are often used in an adjunctive role. Urinary cytology, which involves microscopic examination of voided or barbotaged urine, has a sensitivity of between 4% and 31% for the diagnosis of low-grade disease, with an overall sensitivity and specificity of 34% and 99%.¹⁹ Its sensitivity improves for high-grade disease, particularly carcinoma in situ (CIS); however, cytology may miss up to 60% of high-grade tumors.²⁰

Tumor marker assays have been developed in an effort to improve on cytology for the detection of bladder cancer with variable success. Commercially available tumor marker assays include bladder tumor antigen (BTA), ImmunoCyt, nuclear matrix protein 22 (NMP22), and UroVysion. BTA assays detect human complement factor H–related protein. Results can be impacted by hematuria from other causes. The overall sensitivity and

Table 1 Risk groups by guideline panel			
	Low Risk	Intermediate Risk	High Risk
AUA 2007	Small-volume Ta, low grade	Multifocal and/or large-volume Ta low grade	Ta high grade, T1, Tis
ICUD-EAU 2012	Ta low grade	—	Ta high grade, T1, Tis
NCCN	Ta low grade	Ta high grade	T1 high grade, Tis

Abbreviations: AUA, American Urological Association; ICUD-EAU, International Consultation on Bladder Cancer–European Association of Urology; NCCN, National Comprehensive Cancer Network.

specificity of the BTA stat test have been estimated at 57% to 83% and 60% to 92%, respectively.²⁰ ImmunoCyt combines cytology and immunofluorescence from monoclonal antibodies against carcinoembryonic antigen and 2 bladder cancer-associated mucins. It has a reported sensitivity of 50% to 100% and a specificity of 69% to 79%. False positives are associated with benign prostatic hyperplasia and cystitis, and it is generally only recommended for monitoring rather than diagnosis. NMP22 detects nuclear matrix protein and is approved for use in bladder cancer surveillance as well as detection of cancer in at-risk patients. Sensitivity and specificity have been reported at 47% to 100% and 60% to 90%, respectively. Specificity is markedly decreased with coexistent inflammation or instrumentation, leading to a relatively high false-positive rate that has limited its utility in clinical practice.²¹

UroVysion is a fluorescent in situ hybridization (FISH) assay that detects loss of 9p21 and aneuploidy of chromosomes 3, 7, and 17 and is approved for use in bladder cancer surveillance and detection.²² Sensitivity of FISH is reported at 74% overall and 100% for high-grade disease, outperforming cytology in a meta-analysis with an area under the receiver operating characteristic curve of 0.87 versus 0.63.²³ FISH has been associated with the additional benefit of anticipatory positives; multiple studies report the development of cancer within 12 months in a high percentage of cases that seemed to be false positives based on initial cystoscopy.^{24,25} The weakness of FISH relative to cytology is its high rate of false positives, which can be improved by combining with cellular morphology. Nonetheless, the specificity when combined with morphology is only 65%.²⁶ Similar to FISH, several markers designed to detect specific gene mutations common that are common in bladder cancer have shown promise but at this time are still investigational.²⁰

Photodynamic agents including 5-aminolevulinic (5-ALA) acid or hexaminolevulinate (HAL) are approved in 26 European countries for the detection of bladder cancer. Neoplastic cells preferentially uptake these agents and fluoresce in the red part of the spectrum under blue-violet light excitation. A meta-analysis by Kausch and colleagues²⁷ concluded that combined with white-light cystoscopy, the use 5-ALA or HAL resulted in the detection of 20% more tumor-positive patients with NMIBC and 39% more with CIS. The odds of residual tumor being found were significantly less with photodynamic agents than with white-light cystoscopy alone (odds ratio 0.28; 95% confidence interval 0.15–0.52), and recurrence-free survival was significantly higher at 12 and 24

months. Photodynamic agents are not yet part of routine practice in the United States; however, several ongoing clinical trials will help define its role in bladder cancer diagnosis and surveillance in future practice (www.clinicaltrials.gov).

Upper tract imaging is indicated in the context of gross or microscopic hematuria not explained by obvious underlying causes, such as active infection, menstruation, or recent instrumentation.²⁸ Historically, intravenous urography (IVU) was the imaging study of choice for its availability and cost. It is estimated to detect up to 60% of known bladder tumors and approximately two-thirds of upper tract lesions.^{29–31} IVU has, however, been almost entirely replaced by other imaging modalities for the evaluation of the upper tracts.³² Ultrasound avoids ionizing radiation, although its sensitivity is poor for the detection of renal pelvis tumors, and it does not evaluate the ureters. Its sensitivity for the detection of bladder tumors is highly variable, having been reported at 26.0% to 91.4%.^{32,33} Three-dimensional virtual and contrast-enhanced sonography may provide additional benefit for tumor detection within the bladder; however, the clinical utility of these modalities is unclear.^{34,35}

Computed tomography (CT) and CT urography (CTU) have become the American College of Radiology's test of choice for the evaluation of the upper tracts in hematuria.³⁶ In a study by Turney and colleagues,³⁷ in 200 patients with hematuria with a cancer prevalence of 24% on cystoscopy, CTU had a sensitivity, specificity, and negative predictive value of 93%, 99%, and 98%, respectively. The sensitivity for the detection of bladder tumors seems to be best in patients with gross hematuria.³⁸ CTU can fail to pick up smaller tumors (<5–10 mm) and has limited ability to distinguish cancer from mucosal changes related to recent cystoscopic procedures.^{39,40} Renal impairment can prevent the use of contrast in CTU, which limits its utility in this setting.

Gadolinium-enhanced magnetic resonance imaging (MRI) urography may be even better than CTU for tumor detection, with one head-to-head study reporting sensitivity of 93% versus 100% for CTU versus MRI urography and another suggesting superior ability to detect small (<10 mm) tumors.^{41,42} Diffusion-weighted MRI seems to have further advantages over standard MRI in the detection of lesions and in distinguishing benign from malignant disease.^{43,44} Although MRI does have the advantage of avoiding ionizing radiation, contrast administration is, as in CT, limited in those with poor renal function (estimated glomerular filtration rate <30 mL/min).³² Its relatively higher cost and lack of availability have also limited its

use in clinical practice relative to CTU; however, given its advantages relative to CT in local staging, the use of MRI is increasing in some centers. Virtual cystoscopy with either CT or MRI, although an interesting concept, is associated with a higher cost and increased radiation exposure relative to conventional CT and has no role in routine workup of hematuria.⁴⁵

LOW-RISK DISEASE

Low-risk disease is defined by the AUA's guidelines as small, solitary, low-grade, primary disease.⁴ Differing slightly from the AUA, as evident from **Table 2**, the International Consultation on Bladder Cancer–European Association of Urology's (ICUD-EAU) guidelines and the NCCN's Clinical Practice Guidelines in Oncology (NCCN's guidelines) define low-risk disease as Ta low grade.^{5,6}

Approximately 20% of NMIBC presents as Ta low-grade disease, with an additional 20% presenting as papillary urothelial neoplasm of low malignant potential (PUNLMP) and 10% as papilloma.⁴⁶ Papillomas are urothelial outgrowths with otherwise completely normal urothelium and cellular architecture. A PUNLMP is defined by orderly but slightly altered cellular architecture with minimal nuclear atypia.⁴⁷ Papillomas and PUNLMPs are essentially benign lesions; however, distinguishing these entities from low-grade urothelial carcinoma can be challenging for pathologists less familiar with the changes made in the 2004 World Health Organization/International Society of Urological Pathology's consensus classification. Additionally, the potential for a small focus of cancer within or adjacent to one of these lesions means the rate of progression to invasive disease is close to but is not zero.

The consensus from the guidelines of the AUA, NCCN, and EAU for initial management involves complete transurethral resection (TURBT) of the lesion.⁴⁻⁶ For lesions appearing superficial, small, and low-risk, a deep resection may not be necessary. Removal of the lesion with biopsy forceps or with a superficial swipe with the resectoscope loop provides an adequate specimen for pathologic review without exposing patients to the attendant risks of bladder perforation and bleeding.⁴⁸

Following TURBT, consideration may be given to a single perioperative dose of intravesical chemotherapy. The EORTC's meta-analysis concluded that this practice was associated with a 12% reduction in tumor recurrence and a 39% reduction in the odds of recurrence.⁴⁹ This finding was reportedly independent of the agent selected.

The AUA's meta-analysis concluded there was a 17% absolute reduction in recurrence relative to TURBT alone across all risk groups.⁵⁰ Evidence suggests, however, that the benefit of single-dose perioperative intravesical chemotherapy is limited for multiple or recurrent tumors⁵¹ or in cases of high-grade disease when BCG therapy is planned.⁵² The AUA's guidelines, therefore, recommend a single, immediate postoperative instillation of intravesical chemotherapy only for those with apparent low-risk NMIBC. If NMIBC is confirmed following TURBT, surveillance should consist of periodic cystoscopy with neither duration nor interval defined.

The ICUD-EAU's guidelines state that single intravesical administration of mitomycin C or epirubicin should be offered immediately after TURBT for apparent low-risk disease. Induction chemotherapy with or without maintenance may be offered to these patients for "unclear but potential" benefit.⁵ Routine upper tract images are not recommended for isolated Ta low-grade disease, and surveillance is limited to periodic cystoscopy.

The NCCN's guidelines recommend consideration of single-dose postoperative intravesical chemotherapy in the setting of low-grade Ta disease.⁶ Upper tract imaging is recommended for staging, and surveillance cystoscopy should be done at 3 months and then increasing intervals as deemed appropriate.

Adverse events following single-dose postoperative chemotherapy instillation have been reported in up to 22% of cases. Although most of these are mild, serious side effects and rarely death have been reported in cases of unrecognized bladder perforation.⁵² Because 50% to 70% of low-grade Ta lesions recur but only 5% progress, expectant management of low-grade recurrence is advocated by some investigators.^{8,53}

At the authors' institution, they do not routinely use single-dose postoperative chemotherapy based on the risks relative to the modest benefits. If following the initial TURBT there is no tumor at the 3-month in-office surveillance cystoscopy and cytology is negative, the authors perform repeat office cystoscopy 9 months later. Provided there is no recurrence, patients will undergo cystoscopy every 6 to 9 months for 5 years. Upper tract imaging is only performed if patients have symptoms or hematuria.

INTERMEDIATE-RISK DISEASE

AUA index patients with intermediate-risk disease have multifocal, recurrent, and/or large-volume Ta low-grade UC.⁴ The NCCN guidelines consider Ta high grade as intermediate-risk, whereas the

Table 2
Individual panel recommendations, stratified by risk group

	Low-Risk	Intermediate-Risk	High-Risk
AUA 2007	• TURBT or biopsy with complete eradication of all visible tumors • Single instillation of intravesical chemotherapy immediately postoperatively (recommendation)	• Induction course of intravesical BCG or mitomycin C • Maintenance BCG or mitomycin C (option)	• Repeat TURBT if T1 and muscularis propria not sampled • Induction course of intravesical BCG followed by maintenance (recommendation) • Cystectomy (option)
ICUD-EAU 2012	• TURBT with complete resection of all tumors; repeat TURBT if unsure of completeness of resection • Immediate post-TUR intravesical chemotherapy by instillation of mitomycin C or epirubicin	—	• TURBT with complete resection of all tumors; repeat TURBT if unsure of completeness of resection • BCG instillation in patients with pTa high grade urothelial carcinoma • For T1 disease ◦ BCG following repeat TUR with initial diagnosis ◦ Cystectomy for high-risk T1 and BCG failures
NCCN	• TURBT • Adjuvant treatment • BCG (option) • Mitomycin C (option) • Observation (option) • Repeat TURBT if incomplete^a	• TURBT • Repeat TURBT if incomplete, no muscle in specimen, large or multifocal^a • Adjuvant treatment • BCG • Mitomycin C (option) • Observation (option)	Tis • TURBT + multiple selective and/or random biopsies • Prostate urethral biopsy (option) Adjuvant treatment • BCG T1 • TURBT • Cystectomy (consideration) • Repeat TURBT (if no cystectomy)^a Adjuvant treatment • No residual ◦ BCG (preferred) or mitomycin C • Residual disease ◦ BCG or cystectomy T1 with particularly high-risk: multifocal, LVI, BCG refractory • Cystectomy (recommendation)

Abbreviations: BCG, bacillus Calmette-Guérin; ICUD-EAU, International Consultation on Bladder Cancer–European Association of Urology; LVI, lymphovascular invasion.

^a Within 6 weeks.

ICUD-EAU's guidelines do not explicitly define an intermediate-risk category.^{5,6}

The AUA recommends complete TURBT followed by an induction course of bacillus Calmette-Guérin (BCG) or mitomycin C, with a meta-analysis suggesting a decrease in recurrence risk

of 24% and 3%, respectively, versus TURBT alone.⁴ Maintenance BCG or mitomycin C is an option, with meta-analysis demonstrating reduction in recurrence by 31% and 18%, respectively, versus induction therapies alone. The investigators note, however, that the surgeon must balance

this benefit with the cost and side effects of therapy. The AUA's guidelines emphasize that it is unclear if any intravesical therapy decreases the rate of progression.

The NCCN guidelines advocate complete TURBT for Ta high-grade disease (NCCN intermediate-risk), with repeat TURBT within 6 weeks if the tumor is large, multifocal, or incompletely resected or if muscularis propria is absent from the specimen.⁶ BCG induction is the preferred adjuvant treatment, with mitomycin C or observation provided as options. BCG induction therapy should be initiated within 4 weeks of TURBT, with a maximum of 2 induction courses. The investigators note that some data suggest maintenance therapy is beneficial. In cases of bacteriuria, gross hematuria, and traumatic catheterization, BCG should be withheld; for severe local symptoms, dose reduction is encouraged. Surveillance cystoscopy and cytology are indicated every 3 to 6 months for 2 years, then increasing as appropriate with consideration of upper tract imaging every 1 to 2 years. Urinary marker studies are optional.

The authors' institutional preference for surveillance in intermediate-risk disease is cystoscopy, cytology, and reflex FISH (ie, if cytology is atypical) every 3 months for 2 years, every 6 months for 2 years, and then annually thereafter. Routine surveillance is stopped if patients have been completely recurrence-free for 5 years. The authors obtain upper tract imaging only if warranted by symptoms and/or hematuria. Intravesical BCG or chemotherapy with maintenance is selectively given to those patients with multiple, multifocal recurrences requiring TURBT.

HIGH-RISK DISEASE

The AUA's and the ICUD-EAU's guidelines include Ta high-grade (approximately 20% of pTa disease is high grade⁵), T1, and Tis cancers as high-risk disease, whereas the NCCN's guidelines include only T1 high grade and Tis.⁴⁻⁶

According to the AUA's algorithm, a repeat TURBT should be performed in patients considering a bladder-sparing option with T1 disease but no muscularis propria on initial TURBT.⁴ This algorithm is consistent with the findings of Herr⁵⁴ who showed that patients with T1 or Ta high-grade tumors, with or without concomitant CIS, who underwent restaging TURBT had an improved response to BCG and decreased recurrence rates. For those pursuing a bladder-sparing approach and pathologic Ta high-grade, Tis, and/or T1 disease, an induction course of intravesical BCG followed by maintenance BCG is a recommendation, with a meta-analysis suggesting a 5-year

recurrence rate of 34% for those receiving TURBT and BCG maintenance versus 62% for those with TURBT and mitomycin C maintenance. Up-front radical cystectomy with pelvic lymph node dissection is provided as an option. Patients with recurrent disease after prior intravesical therapy but without sampling of muscularis propria should undergo repeat resection (standard) before further intravesical therapy. The panel recommends cystectomy as the preferred treatment of patients with recurrence of Ta high grade, Tis, and/or T1 after previous intravesical therapy for high-risk disease. Intravesical therapy is an option that may be appropriate for those with late recurrences, but it also may put those at high risk for progression at risk for metastatic or muscle-invasive disease.

The 2012 ICUD-EAU's guidelines state that TURBT with complete resection of all tumors should be performed; repeat TURBT should be done if uncertainty of complete resection exists; upper tract imaging should be obtained; and in the case of CIS, narrow-band cystoscopy should be performed if available.⁵ Going forward, there may be a role for the routine use of photodynamic agent-assisted cystoscopy in this setting. For patients with Ta high-grade disease, BCG instillation should be initiated. BCG is recommended for patients with Tis, with at least 1 year of maintenance recommended. For those with T1 disease desiring a bladder-sparing approach, BCG following repeat TURBT should be administered. Cystectomy should be offered for those with high-risk T1, with the risk of progression based on tumor grade, size, and number, timing of recurrence, concomitant CIS, involvement of the prostate, depth of lamina propria invasion, and micropapillary or nested variants. Patients with persistent or recurrent high-risk disease after BCG should also be offered cystectomy.

The response to BCG should be assessed at 3 months, per the ICUD-EAU; those with no response may be offered cystectomy, a second 6-week induction course of BCG, or 3 weekly boosters.⁵ For those with BCG failure (defined as disease after induction at 6 months and maintenance 3 months later), cystectomy is deemed the gold standard. The best option for both BCG-resistant disease (defined as persistent disease 3 months after the induction cycle) and BCG-relapsing disease recurring after a disease-free period of 6 months is repeat TURBT followed by BCG.

The NCCN's guidelines are concordant with the other two guidelines, recommending BCG for Tis disease, noting that some data suggest maintenance therapy provides a benefit.⁶ The NCCN

recommends TURBT with multiple selective and/or random biopsies and mentions prostatic urethral biopsy as a diagnostic option. For T1 high-grade disease, repeat TURBT within 6 weeks is recommended in patients pursuing bladder-sparing treatments while cystectomy is a consideration. Patients with no residual disease at repeat TURBT should preferentially be offered BCG, with mitomycin C listed as an option; those with residual disease may be offered either BCG or cystectomy. Surveillance cystoscopy and cytology should be offered every 3 to 6 months for 2 years, then at greater intervals as appropriate with upper tract imaging considered every 1 to 2 years. Urinary marker studies are optional. Lastly, for patients with T1 disease at particularly high risk of progression (multifocal, BCG refractory, and/or with lymphovascular invasion), cystectomy is recommended.

At the authors' institution, high-risk disease NMIBC is managed with repeat TURBT followed by 6 weeks of induction BCG if a bladder-sparing approach remains appropriate. One-third dose maintenance BCG is given for 3 doses at 3, 6, and 12 months following repeat TURBT. Cystoscopy, cytology, and reflex FISH (for atypical cytology) are performed every 3 months for 2 years, every 6 months for 2 years, and every 9 to 12 months annually thereafter. Upper tract imaging (preferably CTU) is performed on patients with symptoms and/or hematuria, recurrence in the bladder, or every 2 to 3 years.

FUTURE DIRECTIONS

In addition to some of the limitations outlined earlier, additional areas for future investigation remain. One of foremost challenges to the urologist treating NMIBC is deciding when to abandon bladder-sparing therapies in favor of cystectomy. The morbidity of cystectomy is considerable, with short-term complication rates greater than 60%.⁵⁵ However, it is also known that 40% to 50% of patients with Tis will fail BCG,⁵ and nearly 25% will be pT2 or greater and 5.8% pN+ at cystectomy.⁵⁶ For patients with T1 disease, long-term follow-up suggests that roughly one-third will be alive with their native bladder, one-third will be alive having undergone cystectomy, and one-third will be dead of their disease.⁷ When reviewing their experience with cystectomy in patients with Tis, Ta high-grade, and/or T1 disease, Herr and Sogani⁵⁷ found that disease-free survival (DFS) at 15 years was 69% for patients undergoing cystectomy within 2 years of initial BCG therapy versus 26% for those deferring cystectomy more than 2 years. Likewise, Denzinger and colleagues⁵⁸

reported a 78% 10-year cancer-specific survival for patients with T1 disease treated with early cystectomy versus 51% with deferred cystectomy. Although upstaging was found in 30% of cases, no risk factor was found to be predictive.

For patients treated with BCG, Fernandez-Gomez and colleagues⁵⁹ have developed a scoring system to predict recurrence and progression. Their Spanish Urological Club for Oncological Treatment (CUETO) model incorporates age, gender, CIS, and tumor grade, number, T stage, and recurrence to arrive at a risk profile. Similarly, Sylvester and colleagues⁶⁰ used the EORTC's risk tables to formulate a scoring system for the prediction of recurrence and progression in Ta high-grade and T1 disease. The calculator, found at <https://www.eortc.be/tools/bladdercalculator>, factors tumor number, size, recurrence rate, T stage, grade, and presence/absence of CIS. Although these nomograms are helpful in counseling patients, the best time for the abandonment of bladder-sparing protocols remains largely unknown. The study of molecular markers may provide further elucidation of predictive genetic factors for progression and recurrence that has the potential to greatly improve future guidelines.

The duration of maintenance BCG therapy also remains unclear. The Southwest Oncology Group (SWOG) study, the largest to demonstrate the benefit of maintenance BCG therapy, enrolled patients with an increased risk of recurrence, defined as those having 2 or more tumors within 1 year, 3 or more within the last 6 months, and/or CIS.⁶¹ Maintenance BCG, per protocol given at 3, 6, 12, 18, 24, 30, and 36 months, was associated with increased recurrence-free survival. Of note, only 16% of patients received all 7 planned BCG treatment cycles. Because the study constitutes the best available evidence for maintenance usage, by default its regimen is frequently cited. The AUA acknowledges, however, that "the optimal maintenance schedule and duration has yet to be determined."⁵⁰

The role of maintenance BCG therapy is also debated. This point is reflected in the difference between the AUA's and the ICUD-EAU's guidelines, both of which recommend maintenance BCG for high-risk patients, and the NCCN's guidelines, which merely mention that some data suggest a benefit from maintenance therapy.⁴⁻⁶ In contrast to the aforementioned SWOG study and others, Herr's experience has suggested that DFS for patients with high-risk NMIBC treated with TURBT and induction BCG did not improve with the addition of maintenance therapy.⁶²

Lastly, details of timing and duration of surveillance for upper tract recurrence remain ill defined.

Disease has been reported 15 years following diagnosis of lower tract disease.⁶³ In their study of Surveillance Epidemiology and End Results Registry data, Wright and colleagues⁶⁴ found high tumor grade, low tumor stage, and location (orifice, trigone, and bladder neck) to be predictive of upper tract recurrence. At present, the AUA's guidelines simply suggest that periodic upper tract monitoring "is of value,"^{4,50} whereas the ICUD-EAU's guidelines state that periodic surveillance upper tract imaging for patients with Tis is indicated.⁵

COMPLIANCE

Any discussion of guidelines must address the topic of compliance. First, for guidelines to decrease health care costs and improve efficiency, they should be accessible, cost conscious, and evidence based. Udell⁶⁵ showed that a lower-intensity surveillance strategy for patients with low-risk disease can result in savings of nearly \$8000 over 5 years. Such analysis may become more prominent in the construction of future guidelines. Addressing the concern of whether sound, evidence-based medicine is used in guideline construction, Poonacha and Go⁶⁶ evaluated the NCCN's guidelines for the 10 most common malignancies and reported wide variation in the quality of evidence cited. The ICUD-EAU and NCCN currently list the level of evidence and/or consensus beside guidelines, whereas the AUA stratifies its guideline statements by "standard" versus "recommendation" versus "option," thus lending some transparency to their selection criteria.^{4-6,50}

If the implementation of guidelines is lacking, barriers toward adherence must be addressed. Currently, a minority of patients with NMIBC receives guidelines-based care both in the United States and abroad.^{67,68} To improve the implementation of guidelines, Miller and colleagues⁶⁹ have demonstrated the importance of physician awareness of their baseline practice patterns. By first characterizing urologists' preexisting use of radiographic tests for prostate cancer staging before providing education and feedback, the investigators were able to significantly improve the adherence to guidelines.

Lastly, although guidelines serve an important role in patient care, the physician must not forget to address aspects of the patients' care beyond the primary diagnosis and guideline-based algorithm; although smoking cessation may decrease recurrence rates of NMIBC, it will likely harbor an even greater long-term health benefit that should be appropriately emphasized.⁷⁰

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James B. McGeady and Benjamin N. Breyer

This article reviews recent publications evaluating the current epidemiology of urologic trauma. The authors briefly explain databases that have been recently used to study this patient population and then discuss each genitourinary organ individually, utilizing the most relevant and up-to-date information published for each one. The conclusion of the article briefly discusses possible future research and development areas pertaining to the topic.

High-grade Renal Injuries: Radiographic Findings Correlated with Intervention for Renal Hemorrhage **335**

Jeremy B. Myers, William O. Brant, and Joshua A. Broghammer

With the advent of advanced trauma critical care, and precise methods of assessing renal trauma with computed tomography, most patients with high-grade renal trauma can be managed conservatively. Some patients, however, do not do well with conservative management. This article evaluates specific radiographic characteristics that have recently been associated with intervention for renal hemorrhage after trauma.

Damage Control Maneuvers for Urologic Trauma **343**

Thomas G. Smith III and Michael Coburn

This article discusses the evaluation and management of genitourinary system trauma in the critically injured patient. Injuries to any of the organs in the genitourinary system can be managed with a damage control strategy. Often, there is little or no preoperative imaging or injury staging, and these injuries are diagnosed intraoperatively. Finally, specific management strategies of renal, ureteral, bladder, urethral, and genital injuries are discussed.

Strategies for Open Reconstruction of Upper Ureteral Strictures **351**

Richard B. Knight, Steven J. Hudak, and Allen F. Morey

This article presents a review of the literature regarding surgical techniques and outcomes for reconstruction of strictures involving the upper ureter. The preoperative assessment for proximal ureteral stricture is briefly reviewed, followed by a discussion of ureteroureterostomy, transureteroureterostomy, ureterocalicostomy, bladder flaps, downward nephropexy, bowel interposition grafts, onlay or tubular grafting, renal autotransplantation, and nephrectomy. The future direction for reconstruction of the proximal ureter is proposed.

Robotic Reconstruction of Lower Ureteral Strictures**363**

Andrew P. Windsperger and David A. Duchene

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Daniel Ramirez, Jay Simhan, Steven J. Hudak, and Allen F. Morey

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Joel Gelman

This article provides an overview of the open surgical management of posterior urethral disruption injuries. The discussion includes the evaluation of the patient before surgery with a focus on urethral imaging and details of posterior urethroplasty surgical technique.

Primary Realignment of Pelvic Fracture Urethral Injuries**393**

Laura Leddy, Bryan Voelzke, and Hunter Wessells

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Lee C. Zhao, Steven J. Hudak, and Allen F. Morey

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Nathaniel K. Ballek and Christopher M. Gonzalez

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Timothy J. Tausch, Ryan Mauck, Lee C. Zhao, and Allen F. Morey

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Andrew J. Chang and Steven B. Brandes

External genital trauma is uncommon. However when it occurs, it can cause long-term physical, psychological, and functional quality-of-life sequelae. Rapid and proper treatment can help preserve cosmesis and function. Therefore, the treating physician must have a high index of suspicion when evaluating genital injuries. This article reviews the proper initial assessment of the injury as well as the immediate and delayed operative management of genital trauma.

Skin Grafting of the Penis 439

Hema J. Thakar and Daniel D. Dugi III

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PROGRAM OBJECTIVE

The goal of Urologic Clinics of North America is to keep practicing urologists and urology residents up to date with current clinical practice in urology by providing timely articles reviewing the state of the art in patient care.

TARGET AUDIENCE

Practicing urologists, urology residents and other health care professionals practicing in the discipline of urology.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be able to:

1. Review reconstruction of traumatic and reoperative anterior urethral strictures via excisional techniques as well as reconstruction of radiation-induced injuries of the lower urinary tract.
2. Discuss damage control maneuvers for urologic trauma.
3. Recognize advances in diagnosis and management of genital injuries.

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Foreword



Samir S. Taneja, MD
Consulting Editor

This issue of the *Urologic Clinics* is devoted to the field of genitourinary trauma and reconstruction. While reconstructive procedures often are for the correction of anatomic abnormalities arising from iatrogenic and traumatic origin, surgeons subspecializing in trauma are uniquely experienced to provide insight into reconstructive procedures for correction of a wide multitude of etiologies. As such, I am confident the articles provided in this issue will provide a valuable resource for urologists in all types of clinical practice.

Reconstruction of the urinary tract is a mainstay of urologic practice. While we often define reconstructive surgery as a procedure specifically intended to correct a pre-existing problem, the surgical principles arising from our reconstructive procedures can and should influence the vast majority of procedures performed in urology. Reconstructive principles can be applied in oncologic procedures requiring reconstruction following extirpation, general urologic procedures, correction of congenital abnormalities, and in the management of complications arising from urologic surgery.

Similarly, the management of genitourinary trauma offers insight into the management of common challenges arising from renal surgery, lower urinary tract surgery, and secondary surgical complications. We can learn a great deal, for example, on how to manage partial nephrectomy complications through the observation of our colleagues

experienced with both penetrating and blunt renal trauma. While many urologists in practice do not manage acute trauma, almost all are exposed to iatrogenic trauma arising from both urologic and nonurologic surgical procedures.

In this issue, Dr Allen Morey and Dr Steven Hudak have crafted a comprehensive look into the contemporary management of urologic trauma and the strategies for reconstruction of traumatic sequelae. I am deeply indebted to Drs Morey and Hudak for insight into the design of this issue and oversight in its creation. Each of the authors has provided a unique perspective to the principles of reconstruction as they may be applied in different regions of the urinary tract, and in both the acute and the delayed setting. I would like to thank each of the authors for these fantastic articles. I urge the readers to absorb the concepts to take back to everyday practice.

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Preface

Urologic Trauma and Reconstruction



Allen F. Morey, MD



Steven J. Hudak, MD

Editors

During the last three decades, genitourinary reconstructive surgery has evolved dramatically. With increasing numbers of fellowship programs in urologic reconstruction now in existence across the country, expertise is now available in the majority of academic programs and large group practices nationwide. Graduating urology residents now enter the general urologic community with a solid foundation in genitourinary reconstructive surgery as well as minimally invasive surgical techniques. In this issue of *The Urologic Clinics*, we have attempted to present a current, state-of-the-art examination of clinically relevant challenges encountered by urologists managing acute urologic trauma or performing delayed genitourinary reconstruction.

Urologic injury often occurs in the context of severe multisystem trauma, which requires close cooperation with trauma surgeons. The urologist remains an important consultant to the trauma team, helping to ensure that the structure and function of the genitourinary system is preserved whenever possible. Immediate interventions for acute urologic injuries often require flexibility in accordance with damage control principles in critically ill patients. Minimally invasive techniques for

achieving hemostasis have become mainstream among renal trauma patients, and this version of *The Urologic Clinics* identifies important radiographic predictors of those who may benefit from urgent angiographic intervention. The role of robotic surgery, having changed the face of urologic oncology, is now increasingly employed in complex ureteral reconstruction, especially for distal strictures.

The acute management of pelvic fracture-associated urethral injuries remains an ongoing controversy. Primary endoscopic urethral realignment is presented with important recommendations for patient selection and procedural conduct. Many of these patients will ultimately require posterior urethral reconstruction, which remains the hallmark operation for reconstructive urologists, and technical considerations for optimal outcomes are reviewed.

Significant reconstructive challenges often await the urologic trauma patient who has recovered from his associated injuries. Genital injuries are rarely life-threatening, but often become the male trauma patient's chief concern once acute issues are resolved. Plastic surgical principles offer

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an important guide for optimal genital cosmesis and function. Similarly, complex proximal ureteral defects are often not amenable to robotic repair; classic reconstructive techniques, such as Boari flap, ileal ureter, and downward nephropexy, remain commonplace in the robotic era. Finally, although advances in prostate cancer management continue to improve outcomes and decrease morbidity, many men will ultimately encounter negative sequelae from oncologic treatment. Two separate articles in this issue of *The Urologic Clinics* are devoted to the management of 2 of the most challenging iatrogenic conditions facing urologists: radiation-induced lower genitourinary injuries and refractory postprostatectomy bladder neck contractures.

Effective rehabilitation of the urologic trauma patient remains an immensely gratifying undertaking. As the field of genitourinary reconstruction

continues to evolve, we must strive to approach clinical problems in a creative, yet evidence-based manner to ensure optimal outcomes.

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Current Epidemiology of Genitourinary Trauma

James B. McGeady, MD, Benjamin N. Breyer, MD, MAS*

KEYWORDS

• Urologic • Trauma • Epidemiology • Kidney • Ureter • Bladder • Urethra • Genitalia

KEY POINTS

- With 10% of the 2.8 million trauma patients hospitalized yearly in the United States sustaining genitourinary injuries, an understanding of the epidemiology of genitourinary organ injury facilitates prompt diagnosis and appropriate treatment of these injuries.
- The use of national data sets to conduct large population-based studies has increased our understanding of the epidemiology of genitourinary trauma.
- Most renal, bladder, and posterior urethral trauma is from blunt mechanisms, most commonly motor vehicle collisions.
- Most ureteral and anterior urethral injuries are iatrogenic.
- Research and development of safer vehicles along with public efforts and policy to create safer roadways and regulate hazardous driving activities continues to decrease morbidity and mortality from motor vehicle collisions.

INTRODUCTION

The importance of recognizing and appropriately managing urogenital injuries has been appreciated for centuries. Timely identification and management of these injuries is often organ saving, and at times, life saving.

Worldwide, trauma is currently the sixth leading cause of death, accounting for 10% of mortalities.¹ In the United States, more than 2.8 million people are hospitalized as a result of trauma yearly, with estimated costs of \$406 billion annually in medical expenditures and lost productivity.² Trauma has a predilection for young adults and results in the loss of more productive work years than cancer and heart disease combined.³ The urogenital system has consistently been shown to be involved in 10% of patients presenting after trauma and is therefore a significant factor in trauma-induced morbidity and mortality.⁴

Most trauma data from the 20th century were reported from single-institution data sets. With

the expansion of electronic medical records and national trauma networks, national data sets have become a more accessible and significant source of information.

The National Electronic Injury Surveillance System (NEISS), originally created in 1970 by the US Consumer Product Safety Commission, is one example of these national data sets. It has been used primarily to evaluate the magnitude of injury associated with consumer products, but because it provides a national probability estimate of all injury-related US emergency department presentations, it has proved to be a useful tool for evaluating many facets of trauma epidemiology.

More recently, the National Trauma Data Bank (NTDB), created in 1989, has continued to grow exponentially and currently contains more than 5 million records, making it by far the largest national data set available. It has been increasingly analyzed over the last 2 decades, resulting in significant contributions to the medical literature

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and increased understanding of trauma incidence, mechanism, and outcomes.⁵

The Crash Research and Engineering (CIREN) database, which is a multicenter research network developed by the National Highway Traffic Safety Administration, provides detailed crash site analysis and specific occupant injury data to help researchers better understand the mechanisms of injury in motor vehicle collisions (MVC).

Although far from comprehensive, these are several important examples of the major data sets relating to trauma. In the future, as the evaluation and sharing of data become easier and faster, the continued development of more inclusive and refined data sets will enable researchers to probe further into the epidemiology and, hopefully, prevention of trauma.

ORGANS

Kidney

Prevalence/incidence

Renal injury has historically been reported in 1.2% to 3.3% of trauma patients depending on the data

Europe.¹⁰ Penetrating injuries are more prevalent in undeveloped countries and areas with civil unrest. A retrospective, 4-year single-institution study from a hospital serving 13 smaller cities throughout southeastern Turkey, a region with elevated sociopolitical tensions and a gun in every residence for self-defense and hunting, reported 59% (42/71) of renal injuries were secondary to gunshot wounds (GSW).¹¹ Similarly, 75% (130/174) of renal injuries reported by one hospital in Durban, South Africa were from a penetrating source, with 50% (87/174) caused by GSW.¹² Although penetrating renal injury, which is responsible for 16% of renal injuries per review of the NTDB, is much less common than blunt renal trauma, the incidence of civilian GSW is reportedly increasing in the United States, Africa, and some European countries.^{9,13} Of traumatized patients in the United States, the proportion with renal injury was highest in those sustaining injuries from firearms (3.5%), MVC (2.2%), bicycle accidents (1.9%), pedestrian accidents (1.5%), stab wounds (0.8%), and falls (0.5%).⁹

The epidemiology of renal trauma—Summary of multiple series

	Rate of Renal Injury (%)	Number	Blunt (%)	Penetrating (%)	Minor Injuries (%)	Major Injuries (%) ^a	Renal Exploration (%)	Nephrectomy (%)
Seattle ⁷	2.8	154	93.5	6.5	92	8	N/A	3.8
Toronto ¹⁴	3.25	132	95.4	4.6	72	28	7.4	3.2
San Francisco ⁶	N/A	2254	89.8	10.2	91.1	8.9	7.4	0.8
British Columbia ⁸	1.4	227	93.4	6.6	81.7	18.3	7.1	N/A
NTDB ⁹	1.2	6231	81.6	16.0	82.5	17.5	13	7

^a Major injury defined as AAST grades 2 to 5 or ICD-9 code for laceration, parenchymal disruption, or vascular injury.

Data from Wessells H, Suh D, Porter JR, et al. Renal injury and operative management in the United States: results of a population-based study. *J Trauma* 2003;54(3):423–30.

set.^{6–8} A recent population-based study using the NTDB and consisting of 6231 renal injuries found an incidence of 4.9 per 100,000 population.⁹ Like other trauma, renal injuries are also associated with youth and male gender. Renal injuries occurred in patients less than 44 years of age 70% to 80% of the time and almost 75% of these were male.⁹

Mechanism

In the United States, 82% to 95% of renal injuries are secondary to blunt trauma,⁹ slightly less than the 93% observed in Canada⁸ and 97% in

Motor vehicle collisions

MVC account for approximately 70% of blunt renal injuries, with 50.9% involving 2 vehicles, 21.1% involving a solitary vehicle, and 11.1% involving vehicle versus pedestrian.^{15,16} According to the World Health Organization, approximately 1.3 million people die yearly from road traffic accidents, and another 20 to 50 million suffer nonfatal injuries.¹⁷ Ongoing research into preventative measures to lessen solid organ injury has provided insight into the mechanism of renal injury in various MVC scenarios, as well as the effects of multiple automobile safety features.

One of these studies, a recent review of the CIREN database, demonstrated a 45.3% and 52.8% reduction in renal injury during collisions with frontal and side airbags, respectively.¹⁸ In a separate analysis of the same data set, seat belts, which unquestionably decrease overall morbidity and mortality in accidents, have been shown to account for 90% of renal injuries in frontal collisions.¹⁹ Side-door panel/armrest direct impact is the source of renal injury in most side-impact collisions, as is the steering wheel and instrument panel for unrestrained drivers in head-on collisions. Interestingly, although not statistically significant, renal injury was more likely on the right side for restrained drivers and left for restrained passengers, possibly due to the lower/mid abdominal location of the shoulder restraint on the medial side.¹⁹

Bicycles

With 57 million, or 27% of the US population over the age of 16, riding bicycles on a daily basis, injuries sustained from bicycle-related accidents contribute significantly to the trauma population. According to a review of mode-by-mode fatality and travel statistics report from the US Department of Transportation by Pucher and Dijkstra, bicycling is considered 12 times more likely to result in mortality than riding in a car per kilometer traveled, and results in greater than 600 deaths annually.^{20,21} A review of the 16,585 bicycle-related trauma cases in the NTDB noted that genitourinary (GU) trauma occurred in 2% of bicycle accidents (358 patients).²⁰ Renal trauma was the most common type of GU injury in this subset (75%–80% of GU injuries), with bladder and urethral injuries a distant second.^{16,20,22} A review of the NEISS database estimated that 43,542 (95% confidence interval [CI] 36,447–50,363), or 9%, of all GU injuries presenting to US emergency departments from 2002 to 2010 had a bicycle-related injury.²³ Of these injuries, 31% (12,707 [95% CI 9585–15,830]) involved the testicles or scrotum, with renal injury representing only 5% (2158 [95% CI 1360–2956]) of GU injuries presenting to the emergency room.²³ This discrepancy is likely due to the different patient populations represented by the NTDB and NEISS. Patients in the NTDB have injuries significant enough to require hospital admission and therefore are more likely to have a renal injury. The NEISS database, on the other hand, includes all emergency department presentations, most of which are treated in an ambulatory setting, and not surprisingly consist of a significantly higher number of scrotal injuries.²³

Pediatrics

Because of children's weaker abdominal muscles, less ossified and protective rib cage, paucity of perirenal fat, intra-abdominal renal location, and relatively larger kidney-to-body size ratio, they have an increased risk of blunt renal injury.²⁴ Approximately 10% of children presenting with blunt abdominal trauma have a renal injury.²⁵ According to a recent review of the NEISS database, there were approximately 8249 pediatric renal injuries that presented to emergency rooms in the United States between 2002 and 2010. Although renal injuries accounted for only 3.5% of all pediatric GU injuries, it was responsible for 25.7% of hospital admissions in this cohort.²⁶

All-terrain vehicles (ATVs)

The use of ATVs in both the general and the pediatric populations has continued to increase over the last 20 years. Despite government legislation, multiple public awareness campaigns, improved safety labeling, and age-appropriate recommendations from numerous organizations, ATVs are responsible for an increasing number of pediatric injuries and deaths each year. An estimated 28,300 children under the age of 16 years of age presented to the emergency department in 2010 with ATV-related injuries and there have been 2775 reported deaths since 1982.²⁷ Several recent single-institutional retrospective studies evaluated the risk of GU injury in this subset of patients. Approximately 3% to 3.7% of ATV-related pediatric admissions sustained GU trauma, which was overwhelmingly renal in nature (22/23 patients, 96%).^{28,29} In contrast to a previous publication whereby a rollover injury or a blow to the abdomen from the handlebars was the source of renal injury, ejection was identified as the predominant mechanism of ATV-related pediatric injury in these more recent cohorts.^{29,30}

Sports and solitary kidneys

There has been a significant amount of ambiguity regarding the appropriate recommendations for children with solitary kidneys who wish to participate in contact sports. According to 182 responses to a survey sent to 231 active members of the American Academy of Pediatrics in 2002, 68% of these practitioners reported that they recommend patients with a solitary kidney avoid contact sports.³¹

Since 1994, the American Academy of Pediatrics has recommended a "qualified yes" pending assessment for children with solitary kidneys wishing to participate in contact sports.³² In 2012 Grinsell and colleagues³³ used the data collected for the National Athletic Trainers' Association

Injury Surveillance Study, an observational cohort study collected during the 1995 to 1997 academic years, to evaluate the risk of renal injury in contact/collision sports. From 1995 to 1997, more than 4.4 million athlete-exposures, defined as 1 athlete participating in 1 game or practice, were evaluated and 23,666 physical injuries were reported. Eighteen minor kidney injuries, 3 lacerations, and 15 contusions were observed. None of these injuries required surgical management or resulted in known loss of renal function. For boys, football had the highest rate of renal injury (9.2 injuries/million athlete-exposures). Girls had the highest risk of sustaining a renal injury while playing soccer (5.9 injuries/million athlete-exposures). Overall, the risk of renal injury was significantly less than rates of traumatic brain/head/neck/spine injuries and it was concluded that patients with solitary kidneys should be allowed to participate in contact sports.³³

Ureter

Prevalence/incidence

Ureteral trauma is rare. Almost 25 years ago a large single-institution retrospective study reported ureteral injury in 1% of all urologic trauma.³⁴ More recently, a retrospective analysis of the 22,706 GU injuries in the NTDB from 2002 to 2006 found ureteral trauma responsible for 2.5% of GU trauma (582 patients total).³⁵ This significantly increased incidence is attributed to improved evacuation, stabilization, and evaluation methods of trauma patients resulting in increased survival of severely injured patients with improved initial detection of ureteral injuries.³⁵

A recent literature review on ureteral trauma published by Pereira and colleagues³⁶ identified 77 articles with level 3 to 4 evidence. Consistent with the observation that most trauma occurs in young men, the reviewers noted that an average of 83.4% of patients with ureteral trauma were men, on average 23.2 years of age. This male predominance, which is even higher than for overall trauma, may be representative of the strong association of ureteral injuries with penetrating trauma (61%–62%).³⁵

Mechanism/location

A review of the NTDB from 2002 to 2006 noted that penetrating ureteral injuries occur in a significantly younger population than blunt injuries, 27 versus 37 years of age, respectively ($P<.001$), and are more likely to occur in men than blunt injuries (91% vs 73%).³⁵ Interestingly, this review also demonstrated a much higher overall percentage of ureteral injuries from blunt mechanisms than previously published (38% vs 3%).³⁷ Most

penetrating ureteral injuries (88%) were secondary to GSW, whereas most blunt injuries were associated with MVC (50%). A recent 25-year review of ureteral trauma at the San Francisco General Hospital described the location of 38 ureteral injuries as 70% upper, 8% mid, and 22% distal.^{36,38} Most of the upper ureteral injuries were described as short segment losses amenable to repair with a tension-free anastomosis after initial debridement.³⁸

Mechanisms of ureteral injury per NTDB review

	N = 528	Total Cases (%)
Blunt trauma	24	38
MVC	110	19
Pedestrian	25	4
Motorcyclist	18	3
High fall	15	3
Low fall	8	1
Cyclist	3	<1
Other	45	8
Penetrating trauma	358	62
Gunshot wound	316	54
Stab	29	5
Other	13	2

Data from Siram SM, Gerald SZ, Greene WR, et al. Ureteral trauma: patterns and mechanisms of injury of an uncommon condition. *Am J Surg* 2010;199(4):566–70.

Concurrent injuries

Associated injuries are present in 90.4% of trauma patients with ureteral injury.³⁶ This association represents the ureter's approximation to many abdominal and retroperitoneal organs as well as the severity, and often penetrating nature, of the insult needed to cause a ureteral injury.³⁹ Siram and colleagues³⁵ found the colon/appendix (51%) and small intestine (49%) to be the most commonly associated injuries, which is consistent with findings of previous single-institution studies.³⁶ Surprisingly though, their data showed a much greater incidence of vessel injury with penetrating trauma than previously described by Perez-Brayfield and colleagues⁴⁰ (38% vs 13%).³⁵ Congruent with previous single-institution series, Siram and colleagues³⁵ also found a higher incidence of arterial injuries with blunt rather than penetrating trauma (9% vs 5%, respectively). The converse is true for penetrating trauma whereby venous injuries occurred 27% of the time and arterial injuries were seen in 16%. The iliac vessels lie just posterior to the ureters as they enter the bony pelvis and are especially

susceptible to injury at this location, which explains how together they are injured in 28% of penetrating trauma. Not surprisingly, patients with blunt trauma and ureteral injuries are much more likely to have associated orthopedic injuries than penetrating cases (20% vs 1%).³⁵

Iatrogenic ureteral injury

According to the Consensus on GU Trauma statement on diagnosis and management of ureteric injury by Brandes and colleagues⁴¹ and McAninch, gynecologic surgery accounts for greater than half of all iatrogenic ureteric injuries. A systematic review of benign gynecologic surgery estimated that ureteral injury ranged from 0.2 to 7.3 per 1000 surgeries.⁴² Although ureteral injury typically occurs during gynecologic, urologic, urogynecologic, and other pelvic surgeries, it has been reported with something as simple as a Foley catheter placement.^{41,43,44}

The pelvic ureter is involved in 80% of iatrogenic ureteral injuries, making it by far the most commonly involved segment.⁴⁵ The most common types of ureteral injury, in decreasing order of frequency, are ligation, kinking by suture, transection/avulsion, partial transection, crush, and devascularization with delayed necrosis/stricture.⁴¹ Prior studies have identified resection of large pelvic masses, malignant neoplasms, inflammatory disease, laparoscopy, and prior operation or radiation therapy as risk factors for iatrogenic ureteral injury.^{46,47} These injuries generally occur in the distal one-third of the ureter and are not prevented by placement of preoperative stents, although they do assist with intraoperative recognition when they occur.

8565 patients with documented bladder injury. Of the subjects, 75% were men and 57% were under 40 years (mean 38.9 years). A retrospective single-institution study previously found 1.6% of blunt trauma patients had a bladder injury.⁵¹ In 2009 Bjurlin and colleagues⁵² reviewed the 1,466,887 patient records in the NTDB between 2001 and 2005 and found that 3.6% of patients presenting with a pelvic fracture had a concomitant bladder injury. Although men are more likely to engage in risky activities that result in a pelvic fracture, they noted that men and women presenting with pelvic fracture had a similar incidence of isolated bladder ruptures (3.41% vs 3.37%, $P = .848$).⁵² Several large literature reviews have found that extraperitoneal bladder ruptures make up most injuries (55%–78%), with the rest consisting of intraperitoneal (17%–39%) and combined intraperitoneal and extraperitoneal (5%–8%) ruptures.^{53,54}

Blunt bladder trauma

Blunt trauma accounts for most bladder ruptures (51%–86%).^{51,55,56} The 2004 “Consensus Statement on Bladder Injuries” noted that a pelvic fracture increased the likelihood of bladder rupture from 1.6% to 5.7%, which is slightly more than the 3.6% described in the NTDB review.⁵³ A 20-year prospectively maintained database recently reported that MVCs are the most common cause of blunt bladder rupture (50.5%) followed by pedestrians versus automobile (29.1%), and falling from a great height (14.5%).⁵⁵ Pelvic fractures are present 70% (35%–90%) of the time there is a bladder rupture, which demonstrates the strong association between these conditions.^{50,57} Specific pelvic injuries, notably diastasis

Incidence of specific organ injury in patients with GU trauma

	NEISS ⁴⁸	Scotland ⁴⁹	GSW ¹³	MVC ¹⁶	Bicycles ^{20,23}	Motorcycles ¹⁶
Kidney	7.7%	67%	54%	65%	5%–75%	28%
Ureter	N/A	3%	3.8%	0	N/A	0
Bladder	N/A	18%	18.7%	16%	13%	5%
Urethra	N/A	16%	2.9%	2%	9%	3% ^a
External genitalia	74.3%	20%	29.4%	17%	13%–31%	64%

^a Multiple GU organs may be injured in an individual trauma patient.

Bladder

Prevalence/incidence

Due to its protected location within the bony pelvis, bladder injuries are not as common as their renal counterpart, but still occur with both blunt and penetrating trauma. Deibert and Spencer⁵⁰ reviewed the NTDB from 2002 to 2006 and identified

of the symphysis pubis or sacroiliac joints and displaced fractures of the obturator ring or pubic rami, have been shown to be associated with bladder rupture.⁵⁸ Most bladder ruptures without an associated pelvic fracture occur after a hard blow to the abdomen in a person with a distended bladder, often resulting in an intraperitoneal

blowout injury of the bladder dome. The associated mortality rate of 10% to 22% for patients with a bladder rupture demonstrates the high-energy and multisystem trauma that is usually involved.⁵⁶

Penetrating bladder trauma

The percentage of bladder injuries caused by a penetrating mechanism range from 14% to 49% in several large single series and NTDB reviews, with GSW comprising the vast majority (88%, 316/358 patients with penetrating injury).^{50,55} Per a large literature review, penetrating bladder injury is reported in 3.6% of abdominal GSW, 13% of penetrating injuries to the rectum, and 20% of penetrating injuries to the buttock.⁵³

Iatrogenic bladder injury

Iatrogenic bladder injury is not uncommon. It is the most frequently injured organ during obstetric and gynecologic procedures, with a rising incidence paralleling the rise in complexity of the surgery (1.8–13.8 per 1000 surgeries).^{44,59} Other reported miscellaneous causes for bladder injury reported in literature include trocar placement in the emergency setting for diagnostic laparoscopy,⁶⁰ during orthopedic treatment of pelvic fractures with external fixators,⁶¹ and placement of an intrauterine device.⁶²

Operative risk of iatrogenic bladder injury

Injury Type	Frequency per 1000 Procedures
Open radical hysterectomy	14
Laparoscopic-assisted vaginal hysterectomy	13.8
Laparoscopic hysterectomy	10
Vaginal hysterectomy	9
Cesarean section	1.8
Laparoscopic herniorrhaphy	1.6
Mid urethral sling	0.4
Vaginal delivery	0.1

Data from Gomez RG, Ceballos L, Coburn M, et al. Consensus statement on bladder injuries. *BJU Int* 2004;94(1):27–32.

Bladder neck injury

Bladder neck injuries secondary to blunt trauma in prepubescent boys are well described in the urologic literature. The increased prevalence in this age group over adults is thought to be secondary to their undeveloped prostate. Consequently, there is minimal literature beyond case reports describing pelvic fracture-related injuries of the

bladder neck and prostate until Mundy and Andrich recently reported on 15 patients where they described the mechanism of bladder neck involvement as an extension of a primary injury to the prostate and prostatic urethra.⁶³

Urethra

Prevalence/incidence

Urethral injuries are rare in the trauma population, accounting for approximately 4% of GU trauma per several series, but have the propensity to incur substantial long-term morbidity including intractable stricture disease, incontinence, impotence, and infertility.^{49,64} When the urethra is injured, 65% are complete disruptions with the remaining 35% resulting in partial tears.⁶⁵ Men are approximately 5 times more likely to have a urethral injury than women, which is attributed to the longer length and reduced mobility of the male urethra.^{66,67}

Posterior urethral injuries

Posterior urethral injuries associated with pelvic fractures are the most common noniatrogenic urethral injury in industrialized societies and are approximately 4 times more common than anterior urethral injuries.⁶⁸ Depending on the magnitude of trauma, the posterior urethra is initially stretched and then partially or completely disrupted at the bulbomembranous junction.⁶⁹ Continued research into the mechanisms of posterior urethral injury with pelvic fractures as well as the inherent risks/associations of specific fracture types has further advanced the understanding of these injuries. A prospective study including more than 200 men with pelvic fractures demonstrated that combined straddle fracture and diastasis of the sacroiliac joint confer a 24 times higher risk of urethral injury. Straddle fracture alone has 3.85 times the risk and Malgaigne fracture increases the risk by a factor of 3.4.⁷⁰ In a retrospective, nested case-control study of 119 male patients with pelvic fracture and urethral injury, Basta and colleagues⁷¹ found that 92% of the subjects had specific inferomedial pubic bone fractures or pubic symphysis diastasis, with 88% of these being displaced more than 1 cm. Recently, computer-generated models of the pelvis and urethra have allowed a greater understanding of the mechanisms of urethral stretching followed by disruption at the bulbomembranous junction.^{72–74}

Anterior urethral injuries

Blunt injury to the anterior urethra occurs approximately one-quarter as often as posterior injury and is generally a “straddle-type” injury of the bulbar urethra. This type of injury results from

direct trauma to the urethra itself and often results in a partial disruption or, quite frequently, is not initially identified and presents later as a stricture.⁵⁴ Slightly less commonly, the anterior urethra is injured during a fracture of the penis. The incidence of concomitant urethral injury varies geographically, but ranges from 0% to 3% in Asia and the Middle East to 20% to 38% in the United States and Europe.^{75,76} Urethral injuries also occur more commonly with bilateral cavernosal tears.⁷⁷

Penetrating injuries to the anterior urethra are usually secondary to GSW and involve the bulbar and pendulous segments equally.⁷⁸ The urethra was injured in 2.9% of civilian GSW involving the GU system in a retrospective review of 309 patients sustaining GSW in the Henry Ford Medical Center Trauma Registry. Frequently there are concomitant lower extremity and pelvic injuries in these patients (44% and 33%, respectively).¹³

Iatrogenic urethral injury

Perhaps the most common cause of anterior urethral injury is iatrogenic from Foley catheter placement. Although it is difficult to identify the exact number of Foley catheters placed, 24 million are sold to hospitals within the United States annually.⁷⁹ A year-long, prospective, single-institution study at University California, San Diego found catheter-related injuries to occur in approximately 3.2 per 1000 patients, but after implementing

reproductive, physiologic, and psychological damage.

Scrotal and testicular trauma

Although exposed and dependent in nature, the mobility of the scrotum often prevents it and its contents from severe injury. Still, traumatic injury to the external genitalia, including the penis, is seen in 27.8% to 68.1% of all trauma patients with injury to the GU tract according to multiple published series.^{81,82} Blunt trauma accounts for up to 85% of scrotal and testicular injuries, most of which are sustained during athletic activity.⁸³ Scrotal trauma can result in a spectrum of findings ranging from local hematoma to ruptured or dislocated testicles.⁸⁴

Penetrating scrotal trauma, albeit less common, is generally more severe and usually requires surgical exploration. Up to 40% to 60% of penetrating GU injuries involve the external genitalia. In a 30-year single-institution retrospective review of 110 patients with penetrating external genital injuries, Phonsombat and colleagues⁸⁵ found that gunshots account for 55% of penetrating scrotal trauma, with stab wounds/lacerations (42%), and bites (3%) accounting for the rest. Orchiectomy rates range from 25% to 65% depending on the study, with a higher prevalence in lacerations than GSW, likely due to the high propensity of self-inflicted orchiectomies, which are less often salvageable.⁸¹

Review of published series on GSW trauma to scrotum

Institution	No. of Patients	No. of Injured Testicles (%)	No. of Nonoperative Management (%)	No. of Orchiectomies (%)
Temple Univ. ⁸¹	97	50 (54.9)	6 (6.2)	24 (48)
UMDNJ ⁸⁶	62	33 (61.1)	8 (12.9)	20 (60.6)
UCSF ⁸⁵	40	24 (60)	0 (0)	6 (25)
LSU ⁸⁷	27	23 (85.2)	0 (0)	15 (65.2)
UCLA-Harbor ⁸⁸	19	4 (66.7)	13 (68.4)	2 (50.0)
Wash. Univ. ⁸⁹	17	17 (100)	0 (0)	6 (35.3)

nursing education programs on Foley catheter placement, they showed a decrease in incidence to less than 1 per 1000 patients, illustrating the value of these preventative measures.⁸⁰

External genitalia

Due to the external location of the male genitalia, they are relatively exposed and vulnerable to trauma. Although not generally life threatening, genital injury is relatively common. Prompt attention is warranted to limit long-term sexual,

Penile trauma

Penile trauma is less common than scrotal/testicular trauma, but still comprises 10% to 16% of GU injuries per several single-institution series.⁹⁰ In one large civilian study, penetrating penile trauma accounted for 33% of all penetrating genital trauma (scrotum = 48%).⁸⁵ Associated urethral injury ranges from 4% to 24% depending on the study and mechanism. Stab wounds/lacerations seem to have a higher likelihood of involving the urethra than GSW.^{13,85}

Penile fracture is an uncommon and likely underreported injury, accounting for 1 in every 175,000 emergency room visits.⁹¹ Still, according to the National Inpatient Sample, a nationally representative weighted sample of hospital admission data, there were 1043 men admitted to US hospitals for penile fracture in 2006 to 2007.⁹² Of the 1331 cases of penile fracture reported in the literature between 1935 and 2001, over half were from the Mediterranean region.⁹³ Mechanism of injury varies geographically. The practice of “taghaandan,” where the erect penis is forcibly pushed down to achieve detumescence, is the most common cause in the Mediterranean region.⁹⁴ In the United States and Europe, most fractures occur after the penis slips out of the vagina during intercourse and thrusts against the perineum or pubic symphysis.⁹⁵ A retrospective chart review of 16 patients presenting to the University of Maryland with penile fracture found that intercourse in stressful situations, specifically out-of-the-ordinary locations (68.7%) and extramarital affairs (43.8%), seems to be a common theme in these patients.⁹⁶

Military trauma

The ever-changing landscape of warfare and the institution of Kevlar body armor have likely affected the mechanism and distribution of GU injury seen in modern combat. Historically, GU injury constituted a small portion of battlefield injuries, ranging from 0.7% to 8%, with renal injury noted in up to 40%.^{97–99} Most of these wounds resulted from bullet injury. Now, projectile fragments from mortar shells, aerial bombs, rockets, and improvised explosive devices account for most modern battlefield urologic injuries.⁹⁷

Recent reports from overseas contingency operations the US Military is currently engaged in have reported similar findings with GU involvement in 2.8% to 5% of injuries.^{98,100} The largest cohort, consisting of 16,323 trauma admissions, reported 887 GU injuries with involvement of the scrotum in 257 (29%), kidney in 203 (22.9%), bladder in 189 (21.3%), penis in 126 (14.2%), testicle in 81 (9.1%), ureter in 24 (2.7%), and urethra in 7 (0.8%).¹⁰⁰ Explosive devices were responsible for 50% to 65% of the injuries; individual firearms caused 15% to 37%, and the remaining 11% to 13% were due to blunt injury, primarily MVC.^{98,100}

The shift in primary mechanism of injury, from penetrating missile to explosive fragments, and the increased use of body armor have changed the spectrum of injuries seen on the battlefield. The higher rate of genital injury (68%) seen in soldiers in recent conflicts is likely because of explosions.^{100,101} The decreased renal and ureteral

injuries are likely a result of protective body armor.^{97,98,102}

RESEARCH FUTURE DIRECTIONS

At the time of establishment of the Centers for Disease Control and Prevention injury center in 1987, only 5 centers, including Harvard University, Johns Hopkins University, University of North Carolina, University of Washington, and Wayne State University, were funded. Today the injury center funds 11 programs, and vast improvements continue to be noted in multiple injury areas. For example, in 2010, 32,885 people died in motor vehicle traffic crashes in the United States—the lowest number of fatalities since 1949 and a 2.9% decline from 2009 (33,883 fatalities).¹⁰³

Continued research and development of safer vehicles along with public efforts and policy to create safer roadways and regulate hazardous driving activities will likely further promote this trend.

The application of computer-generated models based off of human imaging to traffic accident modeling has given us insight into the understanding of the mechanics of posterior urethral injury.^{73,104}

On a different note, the recognition of violence as a public health problem has resulted in multiple evidence-based strategies and programs to reduce violence, especially in youths, and highlighted the cost-effectiveness of monetary allocations aimed at prevention instead of incarceration.¹⁰⁵

As we continue into the 21st century armed with more efficient diagnostic machinery, communication and data storage technology, and tools that enable us to provide more efficient and higher quality patient care, we must continue to advance our understanding of the epidemiology of trauma to better prevent it, and more effectively treat it when it does occur.

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High-grade Renal Injuries

Radiographic Findings Correlated with Intervention for Renal Hemorrhage

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KEYWORDS

• Kidney • Trauma • Renal • Bleeding • Radiology • Model • Computed tomography

KEY POINTS

- Most high-grade renal injuries are managed conservatively. A key to successful nonoperative management is identifying those injuries that need intervention for continued renal hemorrhage.
- The American Association for the Surgery of Trauma (AAST) grading has been modified to decrease disparities in reporting of grades within the renal trauma literature, but there remains a broad categorization of risk for hemorrhage within grade 3 and 4 injuries.
- Specific radiographic parameters may serve as identifiers for patients at risk of continued renal hemorrhage.

BACKGROUND

Epidemiology of Kidney Injury

Renal injuries are relatively uncommon and are present in about 1% of patients hospitalized after traumatic injury.^{1–3} Of all genitourinary trauma, however, the kidney is by far the most commonly injured organ in civilian institutions.^{2,4} Extrapolations based on large renal trauma series estimate there to be an annual incidence of 245,000 traumatic renal injuries worldwide.⁵ In large population-based studies, blunt injury is the leading mechanism of injury and accounts for between 81% and 95% of cases.^{3–5} The mechanism of trauma can vary significantly, however, and single institutional series in urban centers demonstrate a much greater predominance of penetrating injury to the kidney.⁶ Although the incidence of renal trauma is lower compared with other solid organ injuries regardless of the mechanism, these

injuries can be associated with life-threatening complications of which renal hemorrhage is the most acute and dramatic.

Conservative Management of High-grade Injuries

Multiple studies have shown that high-grade renal trauma can be successfully managed in most cases conservatively.⁷ This is true even in cases of penetrating trauma in patients that do not require laparotomy for other abdominal injuries, have undergone appropriate radiologic imaging, and have adequate renal injury staging.⁸ The absolute indications for renal exploration are life-threatening hemorrhage from renovascular injury; ureteropelvic junction avulsion; and urinoma unresponsive to minimally invasive procedures (ureteral stenting or perinephric drainage). The relative indications for exploration are laparotomy

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for other abdominal injuries, concomitant pancreatic⁹ or bowel injury,¹⁰ and large devascularized segments of kidney.¹¹

The importance of nonoperative management of renal injury is avoiding laparotomy and more importantly avoiding iatrogenic or unnecessary nephrectomy. At trauma centers with interest in renal trauma, nephrectomy is rare and reserved for renovascular injuries.¹² However, nationally studies have shown that the most common operation in the management of renal trauma remains nephrectomy.^{1,2} In series where nonoperative management has been rigorously adopted, nephrectomy in high-grade renal trauma has dropped and proportionally renal salvage has risen.^{13,14} It is intuitive and actually observed that after trauma nephrectomy renal function is halved,¹⁵ although it is debated whether this leads to worse outcomes.¹⁶ Despite this debate, it is obvious to any trauma surgeon that unnecessary nephrectomy in the setting of severely traumatized patients is harmful.

Because the most common management of renal injury remains nephrectomy,¹⁷ conservative management of renal injuries, often with angioembolization when feasible, has been shown to decrease the rate of nephrectomy and increase renal salvage.

CURRENT GRADING OF RENAL INJURY

The American Association for the Surgery of Trauma (AAST) organ injury severity scale is the gold standard for assessment of traumatic renal injuries since its inception in 1989,¹⁸ and it has been shown by multiple studies to provide excellent prognostic information.^{19,20} The AAST grading scale, however, is very broad and there is a large spectrum of risk for complications, such as renal hemorrhage within AAST grade 3 and 4 injuries. In addition, there is significant discrepancy in grading between AAST grade 4 and 5 injuries within the literature. One reason this grading subjectivity arises is because of the ill-defined AAST grade 5 “shattered kidney.” Many severe grade 4 injuries are categorized as grade 5 injuries because of this designation of “shattered kidney.”

Modifications of AAST Grading

To eliminate this discrepant grading of renal injury prevalent throughout the trauma literature, Buckley and McAninch²¹ recently proposed changes to the AAST grading system. The authors proposed that grade 5 injuries should include only those injuries that involved a main renal artery or renal vein injury and would cause in most cases total devascularization of the kidney by either renal hilar avulsion or an obstructive intimal arterial

flap (**Fig. 1**). Examples of grade 4 and 5 injuries with the modified AAST grading system, referred to by the authors as the revised Renal Injury Staging Classification (RISC), are illustrated in **Fig. 2**.

Adopting the revised RISC means that most injuries that demonstrated any vascularized and viable kidney are designated as a grade 4 injury. These changes expand the breadth of grade 4 injuries and also increase the spectrum of hemorrhage risk in grade 4 injury, the subject of this article. It is very important to understand the discrepancies in the reported outcomes of high-grade renal injury within the literature to interpret the results from published series including prognostic nomograms and models.

Although the revised RISC encourages uniform reporting and a greater ability to compare results between studies, it does not increase the prognostic value of the system and the grade of renal injuries still remains very broad. When Buckley and McAninch²¹ applied their proposed modifications to the large series from San Francisco General Hospital they found that only 2 of 52 patients with grade 5 injuries were downgraded to grade 4 and the changes made very little difference in the renal salvage rate (4.3% vs 4.2% in grade 5 injuries). However, this series was graded with a prejudice toward the modifications suggested in the recent article throughout its maintenance over the last four decades. In other series, such as Altman and colleagues,²² where a salvage rate of grade 5 injuries was 46%, there is little doubt that reclassification of grade 5 injuries into the grade 4 category dramatically decreases the grade 5 renal salvage rates to make them more comparable with San Francisco General Hospital's series.

Thus, although these changes encompassed in the revised RISC may add uniformity within the literature they do little to increase the value of AAST grading to predict renal injuries that fail conservative management. Conversely, they act to broaden the definition of grade 4 injuries and the probable spectrum of clinical behavior of these injuries. Recognizing the wide spectrum of hemorrhage risk within grade 4 injuries, expanded by the revised RISC, highlights the importance of developing a predictive model in high-grade renal injury, especially given the greater contemporary role of conservative management of these injuries.

RADIOGRAPHIC PREDICTORS OF RENAL HEMORRHAGE

Four groups have looked at radiographic findings associated with renal hemorrhage after trauma.

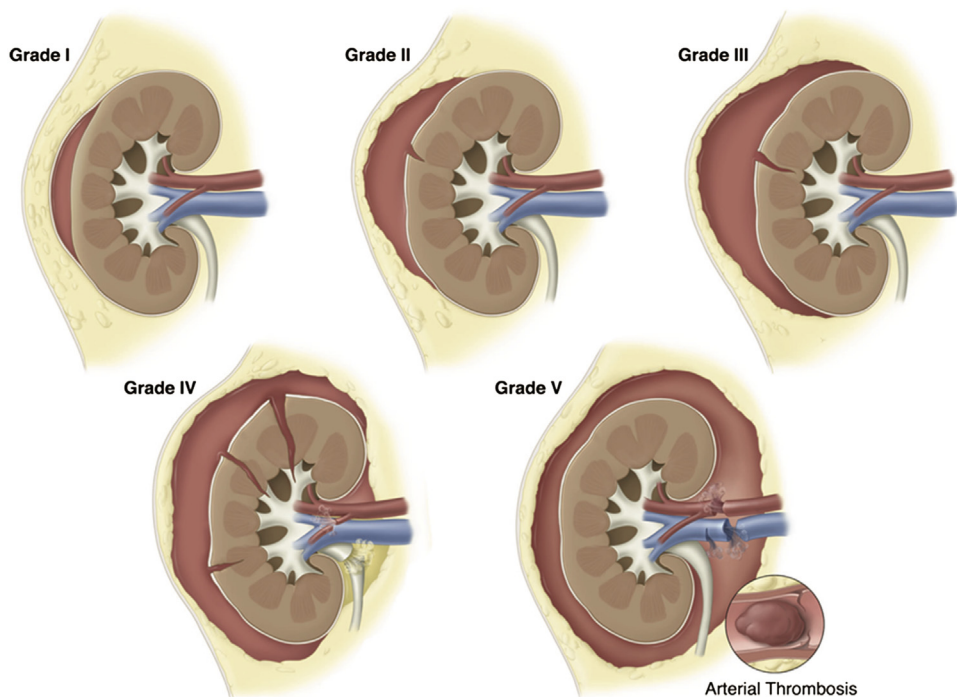


Fig. 1. Modified AAST grading intended to eliminate inconsistent reporting of grade 4 and 5 renal injuries. Grade 5 injuries, with this modification, would consist of those injuries with arterial thrombus or a renal hilar injury, such as renal hilar avulsion. The previous grade 5 “shattered kidney” is now referred to as a grade 4 injury if there is vascularized kidney.

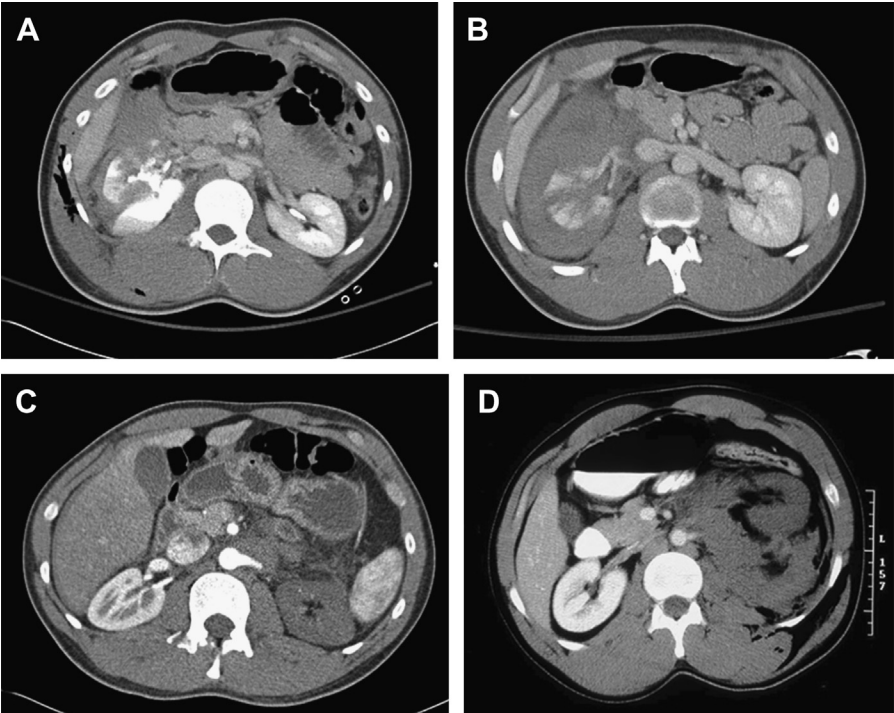


Fig. 2. Computed tomography of modified AAST grading of renal trauma. (A) Grade 4 injury with urinary extravasation. (B) Severe grade 4 laceration previously often categorized as grade 5 “shattered kidney.” (C) Grade 5 injury with intimal flap from deceleration injury. (D) Grade 5 renal artery hilar avulsion. (Courtesy of Dr Jack McAninch, San Francisco General Hospital, San Francisco, CA.)

The first study, by Dugi and colleagues,²³ was reported from Parkland Hospital in 2010. Their patient population included 102 patients with grade 3 and 4 renal trauma, which was caused by blunt trauma in greater than 90% of cases. In patients with AAST grade 3 and 4 blunt renal injuries, they proposed three imaging characteristics that were independent risk factors associated with the need for intervention for bleeding. These included intravascular contrast extravasation; complex laceration (defined below); and perinephric hematoma greater than 3.5 cm.

These parameters were evaluated on the initial computed tomography (CT) scan, which was obtained on presentation to the emergency department. Intravascular contrast extravasation was identified during the arterial phase of the CT scan (Fig. 3). The location of the laceration was determined by drawing a line through the axis of the hilum of the kidney in cross-section and then drawing another line perpendicular to this, which transected the kidney into approximate quarters (see Fig. 3). Any laceration medial to this perpendicular line was classified as a medial laceration. Patients that had both a medial and a lateral laceration were classified as having a complex laceration. Perirenal hematoma distance was

determined on the CT scan cross-section by the maximum measurement of the edge or rim of the hematoma from the capsule of the kidney on the CT scan cross-section (see Fig. 3).

The three risk factors in this study were all significantly independently associated with need for intervention for hemorrhage. Intravascular contrast extravasation, a complex laceration, and a perirenal hematoma distance greater than 3.5 cm increased the odds of intervention for hemorrhage by 13.8, 8.4, and 10, respectively. The authors then assigned 1 point to each of these risk factors and determined a “renal trauma risk score” with a possible score of 0 to 3 points. They found that patients with 0 or 1 points had a risk of intervention for renal hemorrhage of 7% versus 67% in patients with 2 or 3 points. Overall, 18 of the 102 patients required intervention for hemorrhage (8 patients at AAST grade 3; 10 patients at AAST grade 4) and the overall predictive accuracy was 80% of their proposed model.

In a 2011 French study of angiographic intervention for renal hemorrhage after trauma, Charbit and colleagues²⁴ analyzed several CT scan criteria with regard to need for angiographic embolization (either selective or the entire kidney) after renal trauma. Their study included 52 patients that had

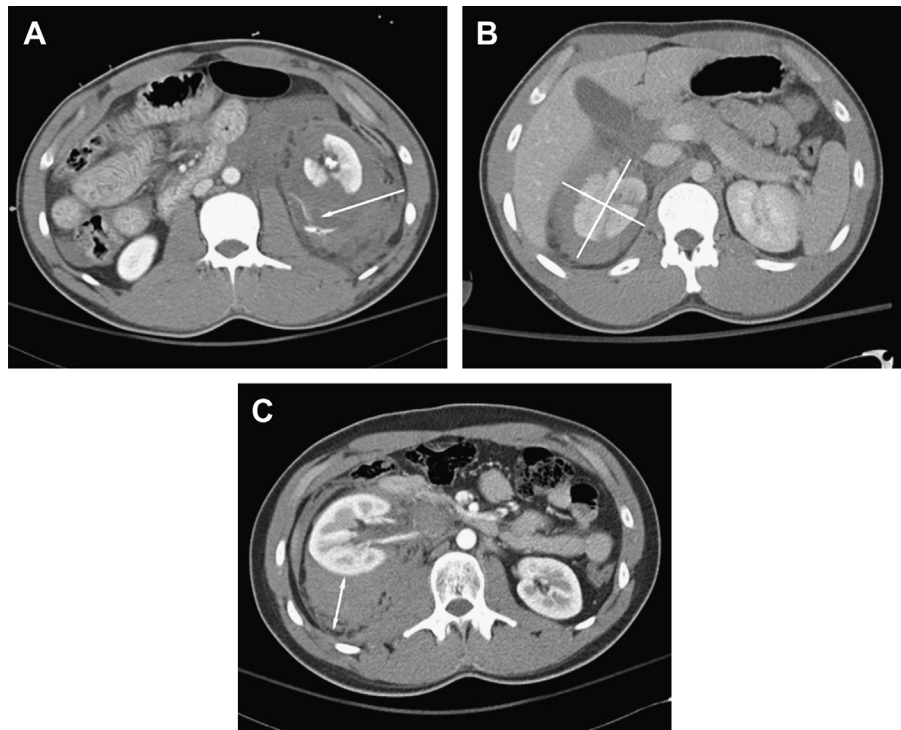


Fig. 3. Computed tomography of radiographic findings associated with intervention for renal hemorrhage. (A) Intravascular extravasation. (B) Both a medial and lateral laceration, classified as a complex laceration. (C) Measurement of a perirenal hematoma rim distance from the renal capsule to the rim of the hematoma.

AAST grade 3 or higher injuries. The predominant mechanism was again blunt trauma in 89%. This study included only angiographic intervention in patients that were managed conservatively and, although all the patients had initial CT scan, five were excluded because they underwent nephrectomy or partial nephrectomy. Of the 52 patients managed conservatively that did not require operative management the authors analyzed the predictive value of intravascular extravasation, perirenal hematoma rim distance, laceration location, and discontinuity of Gerota fascia. All patients at their center who required greater than 2 units packed red blood cells and had intravascular extravasation or a large perirenal hematoma underwent angiography per their treatment protocol. They then tried to retrospectively correlate these and the other CT scan findings to the need for angioembolization.

The authors of this study were unable to correlate many of the CT scan findings with need for intervention with angioembolization. They were able, however, to define a patient group that absolutely did not need angiography and embolization as those that did not demonstrate intravascular extravasation and had a perirenal hematoma rim distance of less than 2.5 cm. This was found to be true despite some of these patients clinically demonstrating ongoing bleeding, which was attributed to other injuries.

In a set of studies from a Taiwanese group, several CT findings were studied to determine the need for angiographic intervention. The first of these studies in 2010 by Fu and colleagues²⁵ examined 26 patients undergoing angiography for blunt renal injury. Hemodynamically stable patients presenting with acute injury underwent CT scans as part of their trauma assessment. All patients with active contrast extravasation on CT underwent angiography and those with persistent bleeding then underwent embolization. The CT findings were reviewed retrospectively to look for predictors of the need for embolization. Of the 14 of 26 patients who underwent embolization, 79% had a disruption of Gerota fascia versus 2% in the nonembolization group. However, disruption of Gerota fascia was not found to be significant by Charbit and colleagues²⁴ in the French series.

In an update of their series, Lin and colleagues²⁶ looked at CT findings in those patients with renal trauma of AAST grade 3 or greater who underwent angiography. The angiography protocol was similar to the 2010 series. A total of 81 patients were included with 22 patients (27%) undergoing embolization. Contrast extravasation, extent of hematoma, and perirenal hematoma rim distance

were all significant predictors of the need for embolization. Extent of hematoma was defined as extending down into the pelvis, across the right margin of the aorta for left-sided renal injuries, or extending across the left margin of the vena cava for right-sided renal injuries. The combination of contrast extravasation and extent of hematoma had the highest predictive value.

The final study originated from our own institution, the University of Utah.¹⁷ In Utah, there are two adult level 1 trauma centers and the data were pooled from these centers. Penetrating trauma is rare in Utah (similar to the Parkland study, where only 5.8% of injuries had this mechanism)²³ and for this reason we excluded patients with this mechanism. We also excluded patients that were taken to the operating room immediately without a CT scan and patients that had grade 5 injuries as defined by the revisions recently suggested by Buckley and McAninch.²¹ We found a total of 115 patients that met the inclusion criteria (blunt injury, AAST grade 3 or 4, CT scan done on presentation). We analyzed the three parameters defined by the Parkland Hospital group and found that intravascular extravasation and a perinephric hematoma rim distance greater than 3.5 cm both were associated with the need for intervention for hemorrhage by 16.4- and 8.4-fold, respectively. The location of laceration in the kidney, however, was not independently associated with intervention for renal hemorrhage, which was different than the findings from Parkland Hospital.

Our data also supported the Parkland Hospital's renal trauma risk score. We found that patients with 0 or 1 point had a risk of intervention of 2.9%, versus 18% and 50% in those patients that had 2 and 3 points, respectively. Our study was different in several important respects from the original Parkland study. We had a very low intervention rate of 7% (eight total patients) compared with 18% in the Parkland study.^{23,24} The angiographic intervention rate was 20% in the French study and 27% in the Taiwanese study.^{24,25} We hypothesized that this likely originated from differences in management regarding initial imaging and differences in threshold for treatment of ongoing hemorrhage. For instance, in the French study all 101 patients with renal trauma had a CT scan on presentation.²⁴ This is very different from our practice where patients with unstable hemodynamics and a positive focused abdominal sonogram for trauma examination are taken immediately for operative exploration without a CT scan. In our study 11 patients out of the 32 that were excluded had nephrectomy or partial nephrectomy. If these patients had

undergone a CT scan before the operating room our intervention rate would have likely been much higher. Another practice variation that could easily account for differences in outcomes between the three studies is how tolerant centers and individual trauma surgeons are to hemorrhage. In the French study patients were taken for angiography if they needed greater than 2 units of packed red blood cells and had either intravascular extravasation or a “large” perirenal hematoma on their initial CT scan. The Taiwanese group had even less stringent criteria for angiography requiring only active vascular contrast extravasation on initial CT scan. Embolization was performed with any signs of bleeding on angiography regardless of transfusion requirements or hemodynamic status.^{25,26} These criteria would be regarded as overly aggressive at many centers, and intuitively would lead to a much higher intervention rate than a more conservative strategy. Another example of different management strategies in regards to ongoing hemorrhage is that 44% (8 of 18) of patients in the Parkland study that required intervention had grade 3 injuries. This is dissimilar to our findings, where we found no patients with grade 3 injuries needed intervention. Another possible factor that could lead to the inconsistencies between the studies is differences in mechanism of injury. For instance, 21% of the patients in our series had sports-related injuries that often produce high-grade isolated renal injuries.²⁷ Patients with isolated renal injury could potentially tolerate more hemorrhage than those with multitrauma that are bleeding from many different sites.

DISCUSSION

All of the radiographic findings that have been explored as potential predictors of dangerous ongoing renal hemorrhage are independent of the AAST grade. These risk factors can be applied to an initial CT scan regardless of whether the AAST grade is correctly assigned. This is important because of the inconsistencies in grading patients with renal injury.²¹ It is also important because in many trauma centers, including our own, correct genitourinary imaging after trauma can be difficult to obtain because of tertiary referral or ongoing management of other injuries. At our institution, only 73% of patients with high-grade renal injury or a perirenal fluid collection had appropriate imaging with an excretory phase CT scan.²⁸ The authors of the Parkland Hospital study, in their paper, proposed that AAST grading be modified to include a 4a and 4b category based on their renal trauma risk score. Those patients

with a renal trauma risk score with 0 to 1 points with a 7% risk of intervention would be classified as 4a and those patients with 2 to 3 points with a 67% risk of intervention would be classified as 4b.

Clinical parameters have also been used successfully to define risk of intervention including renal exploration for hemorrhage independent of presenting imaging characteristics.^{29,30} The ideal predictive model with reliable sensitivity and specificity would likely incorporate clinical and radiographic aspects of trauma patients' presentations to predict their hemorrhage risk and their clinical outcome. For instance an elderly patient with radiographic indicators of continued hemorrhage would likely need to be treated much more aggressively than a young patient with hemodynamic reserve. The same may be true of concomitant injuries. Patients that suffer from multiorgan trauma may not tolerate additional hemorrhage compared with patients with a solitary kidney injury, which is more often seen in sports-related accidents.²⁷

A multi-institution study is needed that incorporates imaging characteristics at presentation and clinical factors, such as shock, presence of acidosis, comorbid state, concomitant injuries, injury severity score, initial hemoglobin, and ongoing transfusion requirements, among other factors to guide trauma surgeons about the need for interventions for continued renal hemorrhage.

SUMMARY

The success of the current movement toward nonoperative management of high-grade renal injuries would be strengthened with a precise and reproducible method of identifying patients at increased risk for renal hemorrhage. Failure of conservative management in the immediate setting is mostly from continued hemorrhage of a high-grade renal injury. A predictive nomogram or model would be invaluable in the setting of conservative management of renal injury and allow stratification of risk for continued renal hemorrhage. Trauma surgeons could then intervene with angioembolization, nephrectomy, or partial nephrectomy if risk of hemorrhage was unacceptably high. A model or nomogram could also help guide referral to tertiary care centers or mandate a higher level of monitoring for hemorrhage in at-risk patients. Several radiographic findings have the potential of adding value in a model that predicts ongoing hemorrhage risk after high-grade renal trauma. Such a future model should also incorporate clinical patient characteristics, which would likely produce the most accurate predictive tool.

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Damage Control Maneuvers for Urologic Trauma

Thomas G. Smith III, MD*, Michael Coburn, MD

KEYWORDS

• Damage control • Renal injury • Ureter injury • Bladder injury • Genital injury • Urine extravasation

KEY POINTS

- Damage control management of urologic injuries is performed in conjunction with the managing trauma team.
- Evaluation and management of genitourinary injuries in a damage control setting requires unconventional evaluation and surgical techniques because of the critical nature of this group of injured patients.
- Renal injury can often be expectantly managed because of containment of hemorrhage by normal fascial anatomy.
- Temporary urinary diversion through externalized tubes and catheters is acceptable and appropriate in the damage control setting.
- Complex genitourinary reconstructive surgery should be delayed until the patient is hemodynamically and metabolically stable for prolonged surgery.

INTRODUCTION

Damage control in the management of multiorgan trauma is a well-established principal in severely injured patients.¹ The underlying objective is patient survival at all costs. Typically, these patients are critically ill and an abbreviated laparotomy is performed to rapidly control life-threatening bleeding or injuries and the patient is temporarily closed and resuscitated in an intensive care unit setting. The clinical hallmark of patients requiring damage control is the triad of hypothermia, metabolic acidosis, and coagulopathy.^{2,3} Since the term “damage control” was coined in 1993 this multiphase patient management strategy has been expanded to include nonabdominal trauma including thoracic, vascular, and neurosurgical.^{1,4} The genitourinary organ system is also well suited

to this style of management in this subgroup of patients.

Over the past 20 years, we have worked to select approaches to management of the urinary system that allow a common patient care philosophy with our trauma general surgeons. Many urologic injuries can be successfully managed with a planned delayed definitive management after initial hemodynamic control and resuscitation including certain renal, ureteral, bladder, urethral, and genital injuries. This article addresses injury selection, initial imaging and injury staging, initial management at damage control, options for definitive management of urologic trauma, and complications of urologic damage control. Additionally, a brief history of damage control and communication and interaction between the urologist the trauma surgeon are discussed.

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HISTORY OF DAMAGE CONTROL

Damage control is a systematic three-phase approach to management of critically injured patients presenting with the lethal clinical triad.¹ These patients typically undergo an initial abbreviated laparotomy to control life-threatening bleeding and fecal contamination (phase 1). This is followed by fluid resuscitation, correction of coagulopathy, and warming in the intensive care setting (phase 2). Then, after the patient is hemodynamically stable, they are returned to the operating room for definitive management of abdominal injuries and closure of the abdominal wall (phase 3). The evaluation of damage control began in the 1980s with the publication of multiple series evaluating a subset of critical patients with severe abdominal injuries.^{5–8} Before this, the traditional concept was that an injured patient is evaluated in the emergency department and is taken to the operating room for a definitive procedure and the abdomen closed. In the 1980s, Feliciano and Mattox began to evaluate abdominal packing for severe liver injuries.^{5,7,9} In a series of 300 consecutive abdominal gunshot wounds, they noted that survival in this group was worse in patients who developed the triad of acidosis, hypothermia, and coagulopathy.⁹ Four years later, Burch and colleagues¹⁰ described an abbreviated laparotomy in 200 patients with this same triad and noted a survival rate of 33%. The term damage control was coined in 1993 by Rotondo and coworkers¹ after their evaluation of 46 patients, 24 treated with abbreviated laparotomy, and found a survival benefit in patients with significant vascular and multiple visceral injuries. Since that time, damage control has continued to evolve as a major trauma management strategy for critically injured patients and has been applied in the civilian and military settings.^{11–15}

GENERAL MANAGEMENT ISSUES

Emergency Department

Evaluation of the urinary system for injury has improved over time so that well-defined indications exist for examination, imaging, and laboratory study of these patients.^{16,17} In general, all hemodynamically stable patients with gross hematuria or those patients with blunt or penetrating mechanism, microscopic hematuria, and an episode of hypotension (defined as systolic blood pressure of <90 mm Hg) require contrast-enhanced imaging.^{17–20} In most modern trauma centers the preferred imaging technique is cross-sectional imaging by computed tomography.¹⁶ In those patients who are not hemodynamically

stable, imaging studies might not be feasible because often these individuals are rapidly transported to the operating room. Although desirable, confirmation of two functional kidneys preoperatively is not always possible in these settings.

Interaction with the trauma service is beneficial for deciding the urgency and necessity of imaging, facilitating the completion and performance of these studies when necessary, and placing and evaluating urinary drainage catheters. We have found that close preoperative collaboration with the trauma surgery team has facilitated the development of preoperative imaging protocols and streamlined intraoperative evaluation and management of urologic injuries.

Communication

In patients with multisystem trauma, successful management demands frequent and effective communication between various entities, especially between the teams of surgical specialties managing these patients. This is especially true in the damage control patient because their overall survival is lower as a result of the frequent triad of hypotension, hypothermia, and coagulopathy.^{21,22}

The optimal time for consultation of surgical subspecialties by the trauma surgery service is “as soon as possible,” irrespective of need for initial support. In our hospital, we are routinely notified in instances of penetrating trauma when the patient has gross hematuria while the patient is still being evaluated in the shock room. When notified at this stage, we can participate in the entire sequence of urinary system evaluation and management from initial recommendations for radiologic studies through possible surgical treatment. Furthermore, we are able to rapidly assist with drainage or diversion of the urinary system and discuss expected outcomes caused by delaying definitive management of the urinary system injuries. Although the trauma service ultimately controls patient management decisions, we believe that our early input allows for more complete patient care and improvement in outcomes in these critically injured patients.

Intraoperative Evaluation

In patients taken emergently to the operating room multiple options exist for evaluation. The “one-shot” intravenous urogram performed in the operating room provides basic information before intervention, namely the presence or absence of bilateral nephrograms.^{23,24} One caveat in this setting is that a hypotensive patient may not have the intravascular volume or pressure to filter enough contrast through the collecting system to

create a nephrogram. A second, less conventional, option is to administer a vital dye, such as methylene blue or indigo carmine, intravenously and atraumatically occlude the ureter of the injured kidney.²⁵ Contralateral function can be confirmed with the collection of discolored urine in the catheter collection bag.

Injuries to the lower urinary tract should not delay urgent intervention when ongoing blood loss creates concern for patient survival. Evaluation of the urethra and bladder can readily be performed in the operating room after significant hemorrhage has been controlled. In patients with suspected urethral injury, options for intraoperative evaluation include cystoscopy or retrograde urethrogram after abdominal exploration. These evaluations should be performed before catheter insertion. The bladder can be evaluated by exploration and bladder distention with retrograde infusion of vital dye or with static stress cystogram after abdominal exploration and control of hemorrhage.

External genital injury is rarely life threatening and does not require preoperative evaluation in the unstable patient. Key considerations are control of hemorrhage with pressure dressing or clamping and suture ligation of bleeding vessels intraoperatively. Hemorrhage control can be performed either concomitantly with abdominal exploration or after life-threatening issues have been addressed.

Intraoperative Hemorrhage

Significant sources of bleeding within the genitourinary system include kidney, bladder, urethra, and genitalia. The specific management of organ-specific injury is discussed later; however, several important considerations merit special mention. Typically, retroperitoneal bleeding in the kidney is confined within Gerota's fascia or the perirenal fascia and can be left undisturbed. Indications for exploration include pulsatile retroperitoneal hematoma or ongoing bleeding through or around the perirenal fascia. Bladder hemorrhage manifests in two forms: extravesical or intravesical. Extravesical hemorrhage can occur into either the pelvis or abdominal cavity by laceration of the perivesical blood vessels or the detrusor muscle. Intravesical hemorrhage occurs from mucosal or detrusor laceration and can cause rapid, profuse gross hematuria. With extravesical hemorrhage, rapid suture ligation of bleeding or perivesical packing with laparotomy pads for control may be necessary. For intravesical hemorrhage, temporary hemorrhage control can be facilitated by catheter occlusion and clot tamponade with correction

or repair after the patient is stable. Genital bleeding is usually controlled with suture ligation, but definitive complex genital reconstruction often requires a future trip to the operating room.

Uncontrolled Urinary Extravasation

Although desirable, early urinary control is important but lower priority in the order of patient management issues. In contrast to uncontrolled fecal contamination, which can result in early sepsis, urine is typically sterile and does not pose this risk. However, ongoing urinary extravasation does create tissue irritation and can cause perinephric, retroperitoneal, peritoneal, or pelvic inflammation.²⁶ Because many techniques of temporary abdominal closure involve vacuum dressing or closed suction drains, often much of the extravasated urine is removed. Additionally, many options for temporary urinary diversion exist that can be rapidly implemented on either the initial exploration or at future surgery. This allows for definitive repair to be delayed or deferred until the patient is hemodynamically stable and reconstructive surgery is appropriate. For upper-tract injuries, an externalized stent can be quickly placed and provide thorough urinary diversion. In lower-tract injuries, such as significant bladder injuries, which cannot be quickly repaired, ureteral diversion stents prevent or lessen pelvic or abdominal urinary extravasation and subsequent inflammatory response.

MANAGEMENT OF SPECIFIC ORGAN INJURIES

Renal Injury

Our approach to intraoperative evaluation and management of renal injuries begins with an assessment of the patient's hemodynamic stability and discussion with the operating trauma service about management goals. Often, a patient undergoing abbreviated laparotomy and damage control management has limited preoperative radiologic evaluation. In these cases, decision-making is based on operative findings and available adjunctive studies. Most renal injuries are amenable to a damage control approach with the exceptions being expanding or pulsatile hematoma and ongoing uncontained hemorrhage. We have found that expectant management is successful and appropriate in those patients who are not hemodynamically stable enough to undergo the necessary reconstruction in salvageable injuries.^{27–29} Additionally, it is common practice in urologic trauma patient management to observe and monitor high-grade renal injuries from blunt mechanism.^{27–30} Our approach in damage control patients is to evaluate but not necessarily explore

a confined retroperitoneal hematoma or hemorrhage. Delayed formal exploration and reconstruction can then be performed in a fully resuscitated and more stable patient.

In those patients with penetrating injuries, the injury is often apparent based on the site of retroperitoneal penetration.³¹ Blunt injuries can be more challenging because the retroperitoneal fascia is often intact and without the benefit of preoperative imaging, the exact location of the injury is more difficult to ascertain. In these patients, evaluation of the hematoma is paramount in deciding which patients to explore. We have observed that retroperitoneal hematomas requiring exploration are relatively easy to identify, usually indicate renal pedicle injury, and are a life-threatening emergency. The most difficult patients to manage are those with an intimal arterial disruption causing vascular occlusion. In those patients without preoperative imaging, the surgeon must decide if the injury warrants exploration and if the patient is stable enough to undergo evaluation and repair of the arterial injury. Often, in patients undergoing abbreviated laparotomy, the patient's condition dictates that unilateral arterial intimal repair be delayed, especially in the presence of a normal contralateral kidney. In these cases, prolonged warm ischemia usually results in irreparable damage and renal loss.

Further retroperitoneal exploration can be performed without disturbing the contained renal hematoma. Central retroperitoneal hematomas (zone 1) are concerning for vascular injuries, namely the aorta and vena cava. If an injury to these structures is suspected, the trauma surgeon can enter the retroperitoneum and leave the confined renal hematoma undisturbed within the perinephric fascia. If the perirenal fascia is violated and renal cortical bleeding is noted, packing the renal fossa tightly with laparotomy pads can salvage the kidney in an unstable patient. At a future operation, the packs can be removed, the wound irrigated, and the injury repaired in the appropriately selected patient.^{25,32}

A risk of damage control management is that ongoing or even life-threatening hemorrhage can occur from the injured kidney while the patient is resuscitated, warmed, and awaits re-exploration and repair. However, our experience has shown that this is not a frequent occurrence and careful monitoring, as in all patients undergoing damage control, is sufficient. In the damage control setting, major renal parenchymal injury can result in urinary extravasation that is difficult to control without significant reconstructive efforts. Our usual approach is to begin with external drainage and plan for management at a future operation. In general, a

brief period of controlled local urinary extravasation is unlikely to result in a significant adverse event or impact overall recovery of the patient.

During phase 2 in the damage control process, which is usually a period of 48 to 72 hours, suspected renal injuries identified in the first laparotomy are staged. In most patients, we obtain cross-sectional imaging with contrast-enhanced computed tomography scans to identify injuries and select patients for subsequent operation and reconstruction or continued expectant management with no plan for operative intervention.^{16,31} Identifying renal injuries that are appropriate for nonoperative management allows the trauma surgery team to concentrate on other critical injuries and does not expose the patient to the potential morbidity of unnecessary renal surgery. The most important point is to fully stage unknown or suspected injuries.

In select patients, adjunct imaging including arteriography may be appropriate. In these situations, arteriography can be diagnostic and therapeutic for renal, vascular, or solid organ injury. In some injured patients, angioembolization is an appropriate and less morbid treatment especially during phase 2 of damage control management. However, emerging data show an overuse of angioembolization in the management of renal injury based on grade of the injury.³³ An individualized approach to the selection of operative versus angiographic control of delayed renal hemorrhage is important and should be based on factors including level of radiologic expertise available, other nonurologic indications, severity of renal injury, and stability of the patient.

In patients who require delayed definitive operative management, the concepts and operative steps are similar to other renal trauma management.²³ We believe that initial hilar control is important and thus the hilum is initially accessed to provide for arterial and venous control. We have also developed an alternative method of vascular control that does not involve individual control of the renal artery and vein.^{19,25} In this technique, vascular control is obtained by bluntly dissecting along the plane of the psoas muscle fascia, adjacent to the great vessels, and directly placing a vascular pedicle clamp on the renal hilum. We have found this particularly helpful in instances where significant or rapid bleeding is noted. Regardless of the method of vascular control used, it is important to avoid unnecessary nephrectomy because of diffuse bleeding from inadequate control of the renal hilum. After vascular control, the kidney is mobilized, the perirenal fascia opened, and the hematoma is evacuated. After the kidney is adequately

exposed, the injury is debrided and definitive repair is performed. We believe that ureteral stenting or nephrostomy diversion should be strongly considered after delayed reconstruction because of the increased risk of postoperative urinary extravasation compared with primary repairs.

Ureteral Injury

Damage control management of ureteral injury is readily applicable for many reasons.^{34,35} Primarily, the risk of bleeding secondary to a ureteral injury is minimal and outweighed by more pressing concerns with other injuries. Additionally, there are many available options for urinary diversion which can be rapidly implemented that preserve tissue quality and anatomic relationships. Finally, ureteral reconstruction can be a challenging and time-consuming endeavor.³⁵ Depending on the level of ureteral injury and the status of surrounding tissues, temporary urinary diversion or adjuvant measures may be the best management option when the patient is unstable and resuscitation in the intensive care unit is necessary.

A ureteral injury can be diverted using any number of small, hollow medical tubes to intubate the ureteral lumen and externalize the open end of the selected tube. Our preference is to use “single-J” stents (Fig. 1), commonly used in elective urinary diversion procedures; however, a Cordis catheter, central line, or feeding tube can be used with equal efficacy if a specific stent is not available. Regardless of diversion method, it is

important to use a guide wire to ensure that the device travels proximally into the renal pelvis. We secure the stent or tube to the proximal ureter using a 3-0 silk suture and only compress a minimal amount of ureteral tissue (1–2 mm). This prevents migration or dislodgement of the stent and at the same time preserves ureteral tissue for future repair. The distal end of the stent is externalized through a stab incision in the abdominal wall and secured to the skin, after which a drainage bag is placed. With the urine diverted in this fashion, renal output can be monitored until the patient can safely return to the operating room for definitive repair. If the stent becomes occluded with blood clots or debris, the free lumen can be gently irrigated with saline until drainage resumes. If there is any question as to the position of the stent, either plain radiographs or injection of contrast confirms the location of the proximal aspect of the stent. In cases of complete ureteral transection, we do not manipulate, ligate, or divert the distal end of the ureter. Usually, urinary reflux is not a concern in injured patients. If the distal ureter is manipulated or ligated this damages the tissue resulting in ureteral tissue loss and affects the future reconstruction of the ureter.

If the patient's condition does not allow for diversion as described previously or no appropriate tube or device is available, an option for management is proximal ureteral ligation with diversion of the urine by a nephrostomy tube typically placed postoperatively in the interventional radiology suite. The ureter can drain freely into the abdominal cavity, if necessary, with urinary drainage by an external drain or as part of the temporary abdominal closure. However, our preferred method of drainage and diversion is an intubated, externalized stent that allows for assessment of renal output and is easy to perform. The initial management of these injuries is certainly within the ability of the managing trauma service. We believe that early urologic consultation is important for evaluation in the initial laparotomy and planning purposes in future reconstructive surgeries.

In phase 3, the stable patient returns to the operating room for reconstruction. We re-evaluate the ureter at that setting to determine the appropriate reconstructive technique, typically either primary ureteroureterostomy (spatulated end-to-end anastomosis) or ureteroneocystostomy (reimplantation into the bladder).³⁵ The former is used for reconstruction of upper and select midureteral injuries and the latter is used for reconstruction of distal ureteral and select midureteral injuries or lower ureteral loss. Other reconstructive techniques may be required (Boari



Fig. 1. Damage control management of upper ureteral laceration sustained from abdominal gunshot wound. A single-J stent is brought out for temporary urinary diversion. The patient was cold, unstable, and coagulopathic; bowel injuries were stapled off acutely. Delayed planned re-exploration with bowel and ureteral reconstruction was safely conducted the next day after vigorous resuscitation.

flap, ileal ureter, and so forth) but these are beyond the focus of this article. Again, use of stents and urinary diversion are encouraged because of the increased likelihood of postoperative anastomotic extravasation in the setting of delayed reconstruction. Furthermore, any injury or repair performed in proximity to an intestinal injury should have tissue separation with either omentum or other tissue interposition techniques (eg, peritoneum) to isolate any postoperative leaks and minimize these potential effects on the repair of nonurologic injuries.

Bladder

On occasion, a patient sustains pelvic trauma with bladder injury, regardless of mechanism, and is too hemodynamically unstable to undergo primary bladder repair. In blunt trauma, this may occur in patients with complex bladder rupture related to severe pelvic fracture and pelvic bleeding. In penetrating trauma, these patients may have multiple pelvic gunshot wounds or a high-velocity missile injury with injury to other pelvic organs (colon) or devastating vascular injuries. Management of extraperitoneal bladder injury from blunt mechanism is well described and most patients managed in this fashion recover completely.^{36,37} Others have described management of select penetrating injuries to the bladder, which are completely extraperitoneal with simple catheter drainage.³⁸ It is appropriate to temporarily drain the bladder with a transurethral Foley catheter or suprapubic cystostomy catheter in the patient undergoing abbreviated laparotomy. For extensive bladder injury, no direct bladder drainage by catheter adequately drains the urine and thus ureteral stents may be passed into the ureteral orifices bilaterally and externalized to divert the urinary output of the kidneys temporarily.

We have used multiple techniques for urinary diversion in unstable patients with complex bladder injuries. The technique described previously is efficient in hemodynamically unstable patients with concomitant bladder and pelvic injuries. Alternatively, we have used a closed suction drain placed in proximity of the bladder and initially left the drain off suction (to allow for a pelvic hematoma to form) and then began suction after coagulopathy and fluid resuscitation has been initiated.

Urethra

Most urologists are familiar with the damage control techniques used in posterior urethral injuries.^{37,39} In these patients, a suprapubic cystostomy tube is placed for initial urinary diversion and then elective repair is completed weeks or months

after the initial injury. In patients with blunt and penetrating posterior urethral injury, we continue to consider early endoscopic realignment after the patient has been fully resuscitated and returns to the operating room. However, regardless of the secondary approach, the management of posterior urethral injuries follows the general principals of damage control management, which is rapid diversion of the urine as a temporizing measure and re-evaluation of the stable patient. Penetrating posterior injuries may require rapid control of bleeding with suture ligation and packing before urinary diversion. We do not believe that significant manipulation of posterior urethral injuries is indicated in the unstable patient and in these injuries the role of the urologist is to obtain bladder access for urinary diversion in the most expeditious and least morbid approach possible. Most are amenable to successful delayed, single-stage, anastomotic repair (**Fig. 2**).

In anterior urethral injuries, patients undergoing abbreviated laparotomy typically either sustain complex or multiple penetrating injuries or complex pelvic or perineal trauma. In those with penetrating injury, suture ligation for control of urethral bleeding may be necessary. Otherwise, the approach in these patients is urinary drainage either with transurethral or suprapubic cystostomy tube drainage and delayed definitive reconstruction.

External Genitalia

Injuries to the external genitalia are rarely life-threatening and thus, damage control is appropriate

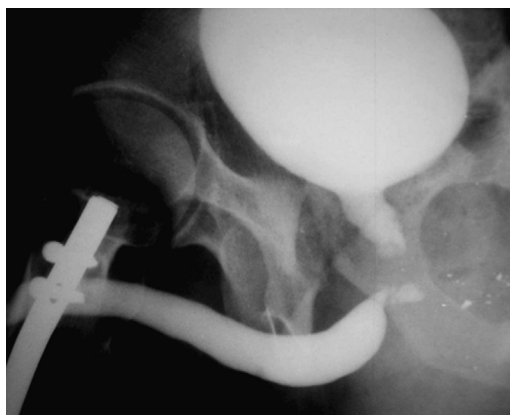


Fig. 2. Delayed management of posterior urethral gunshot wound. Combined retrograde urethrogram and cystogram reveal short obliterative bulbomembranous defect, successfully reconstructed by elective posterior urethroplasty involving excision with primary anastomosis.

in these injuries.^{37,40,41} In multisystem trauma, initial management is compression with pressure dressings and then wound irrigation and limited debridement to preserve tissue for future reconstructive surgery. Arterial bleeding may require suture ligation but these vessels are readily identified in the wound and this step can be performed during the abbreviated laparotomy. Our approach is to limit indiscriminate cauterization and excessive tissue debridement at damage control laparotomy. Determining which tissues are viable long-term is difficult prior to patient resuscitation. Wound vac dressings are an excellent adjunctive measure to be considered for devastating genital skin loss injuries.

COMPLICATIONS OF DAMAGE CONTROL MANAGEMENT FOR UROLOGIC INJURIES

In our experience, complications from delayed repair of renal, ureteral, and bladder injuries are more common than in patients undergoing repair and reconstruction at initial injury presentation. We have two hypotheses about this observation. The delicate urinary tissues become inflamed and edematous following injury making repair more challenging. Injuries that require deferred management may represent more complex wounds and thus are more technically difficult to repair. Based on this, we more frequently use stents and urinary diversion, tissue interposition when possible, and early adoption of antibiotics therapy, especially in those patients with initial external diversion of urine.

SUMMARY

Damage control management of urologic injuries is a technique borrowed from general trauma surgical principles but applicable to the entire urinary system. The objective is to restore normal genitourinary anatomy and function by temporizing ongoing derangements while the critically injured patient is resuscitated and warmed. Often, unconventional evaluation and management is necessary in the phase 1 surgery of damage control and proven urologic techniques can be implemented in the phase 3 surgery. The most important aspects of damage control surgery from the urologist's perspective are communication of the initial injuries and future management plans and availability to assist the trauma service with ongoing patient evaluation. Ongoing outcomes analyses are required to evaluate the best management strategies and identify novel techniques that lessen complications and promote return of optimal genitourinary function.

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Strategies for Open Reconstruction of Upper Ureteral Strictures

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KEYWORDS

• Ureter • Reconstruction • Stricture • Bladder flap • Ileal ureter

KEY POINTS

- The guiding surgical principle during ureteral reconstruction is creation of a tension-free, watertight anastomosis using absorbable sutures that is widely spatulated with preserved blood supply.
- Important factors when planning for ureteral reconstruction include length/location of the stricture, need for bowel interposition, and need to access the bladder.
- Urologists who repair proximal ureteral strictures should be familiar with ureteroureterostomy, transureteroureterostomy, downward nephropexy, ureterocalicostomy, bladder flap, psoas hitch, bowel interposition, and nephrectomy.

INTRODUCTION

Proximal ureteral strictures present a complex challenge to the urologist, often necessitating familiarity with a variety of surgical strategies for management. Because so many options exist for repair of the proximal ureteral stricture, consensus regarding optimal treatment can be elusive. The characteristics of each patient and surgeon's experience combine to determine the surgical plan. When considering the repair of a proximal ureteral stricture, the urologist should be familiar with the techniques listed in **Box 1**. The importance of understanding these surgical approaches is highlighted by the increased incidence of ureteral injury secondary to the advent of ureteroscopy and laparoscopy.¹

Given the retroperitoneal location of the ureter, it is well protected from external trauma. It is

therefore expected that ureteral trauma occurs in only 2.5% of all genitourinary injuries, most of which are caused by penetrating injury (61.5%–96.5%) within the proximal ureter (70%).^{2–4} In the acute trauma setting, it may be necessary to delay definitive reconstruction of ureteral injuries until the patient is stable. This delay may warrant well-established temporary damage control maneuvers, such as externalized single-J ureteral catheter placement or ligation of the proximal ureter with postoperative placement of a nephrostomy tube.⁵

PREOPERATIVE EVALUATION

Numerous patient characteristics must be considered when deciding on the surgical approach to proximal ureteral strictures (**Box 2**). The importance of a thorough patient history and physical examination cannot be overemphasized.

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Box 1
Surgical techniques for proximal ureteral defect

- Ureteroureterostomy
- Transureteroureterostomy
- Downward nephropexy
- Ureterocalicostomy
- Bladder flap
- Psoas hitch
- Bowel interposition
- Renal autotransplantation
- Nephrectomy

A preoperative urinalysis and urine culture are mandatory with antibiotics as indicated. Mechanical bowel preparation should be performed for any patient who may potentially undergo an intestinal substitution of the ureter.⁶ In patients with intact bilateral kidneys, a functional study should be performed to establish differential renal function. Antegrade and/or retrograde ureterography are essential to determine the length and severity of the stricture. Excretory urography (nuclear or radiographic) is helpful in confirming obstruction in equivocal cases. If doubt remains regarding significant ureteral obstruction, a Whitaker test may be performed, although we have rarely resorted to this.

We prefer routinely removing ureteral stents before ureteral reconstruction, thus using a nephrostomy for renal drainage. Removal of ureteral stents allows for delineation of normal versus fibrotic luminal assessment. If the stent is retained

Box 2
Patient characteristics determining surgical approach

- Number of previous failed endoscopic and/or open attempts
- Length of stricture
- Location of stricture
- Function and drainage of each kidney
- History of nephrolithiasis
- Medical comorbidities
- Life expectancy
- History of malignancy
- Previous radiation therapy
- Bladder capacity
- History of inflammatory bowel disease

before surgery, we have found that it may interfere with identification of the stricture.

SURGICAL PRINCIPLES

The guiding surgical principle during ureteral reconstruction is creation of a tension-free, watertight anastomosis using absorbable sutures that is widely spatulated with preserved blood supply, allowing good drainage to the bladder.^{7,8} Maintaining the continuity of the urothelium (ie, avoiding intestinal interposition) is advocated whenever possible for reconstruction of the ureter.^{9–11} The dissection of the nondiseased portions of the ureter should be minimized to avoid disrupting the ureteric adventitial sheath and its vascular supply. However, complete excision of the pathologic portions of the ureter is paramount to prevent recurrent strictures.¹²

The urothelial anastomosis may be wrapped with omentum, peritoneum, or perinephric fat to reduce the risk of leakage and improve the vascular supply. An omental flap is harvested by dissecting the omentum from the greater curvature of the stomach. The resulting omental flap obtains its blood supply from the right or left gastroepiploic vessels.^{13,14}

Depending on the type of reconstruction, retroperitoneal and/or intraperitoneal drainage in combination with ureteral stent placement and bladder drainage are used routinely, but are not always performed.¹³ A passive drain may be preferable to suction drainage to prevent negative pressure on the anastomotic suture line.¹³ We prefer to use both drains and stents.

INCISION

Important factors when planning the incision and surgical approach for ureteral reconstruction include the length/location of the stricture, the need for bowel interposition, and the need to access the bladder. These factors also guide the decision to perform the reconstruction via an intraperitoneal or extraperitoneal approach. If limited proximal ureteral dissection is planned without accessing the bladder, a flank, Gibson, or pararectal incision may be used.¹⁵ A midline incision is preferred for transureteroureterostomy or when the need for bowel interposition is anticipated.¹⁶ However, optimal extraperitoneal exposure of the ipsilateral ureter and bladder may be accomplished through a modified Gibson incision that extends from the tip of the twelfth rib inferiorly in a lazy-S configuration toward the pubic symphysis.¹⁷

URETEROURETEROSTOMY

Ureteroureterostomy is the preferred reconstruction method for short proximal ureteral strictures

if a tension-free anastomosis is possible. It is critical to fully excise the strictured portion of the ureter until healthy epithelial edges are observed.¹⁸ The ureter is either transected obliquely (as initially described by Bovee¹⁹ in 1897) or spatulated for 10 to 15 mm to reduce the risk of anastomotic narrowing and subsequent stricture.^{6,19} Anastomosis is performed with either interrupted or continuous 4-0 or 5-0 absorbable suture.²⁰

Numerous maneuvers may be necessary to provide sufficient ureteral length for a tension-free repair. If the renal pelvis is enlarged, it is possible to achieve additional length by performing a Heineke-Mikulicz transverse incision of the superior and medial renal pelvis with closure in a longitudinal orientation.²¹ The distance achieved with this maneuver is determined by the size of the renal pelvis and the length of the pyelotomy. Renal mobilization and downward nephropexy to the quadratus lumborum or psoas muscle have been shown to provide an additional 4 cm of proximal ureteral length.¹⁸

Although historical reports showed high complication rates from ureteroureterostomy,²² more contemporary series indicate long term patency rates beyond 90% with low morbidity.^{23,24}

TRANSURETEROURETEROSTOMY

The first transureteroureterostomy (TUU) in a human was described by Higgins²⁵ in 1935. TUU is performed by mobilizing the donor ureter proximally, ensuring preservation of the periureteral adventitia. A retroperitoneal tunnel is created across the midline anterior to the great vessels. Placement of the tunnel cephalad to the inferior mesenteric artery may avoid kinking depending on the length of donor ureter available.^{18,26} Mobilization of the recipient ureter is minimized and a 1.5-cm to 2-cm medial longitudinal ureterotomy is made.¹³ In cases involving a short donor ureter, the recipient ureter may be further mobilized toward the midline as necessary.²⁷ The donor ureter is spatulated and the anastomosis is performed with interrupted or running 4-0 or 5-0 absorbable sutures over a stent placed from the donor kidney to the recipient ureter (**Fig. 1**). Some investigators suggest that stent placement into both ureters reduces the risk of stenosis and leakage.²⁸

The length and location of a proximal ureteral stricture determine the feasibility of TUU (ie, the ability for the donor ureter to reach across the retroperitoneum).²⁹ For this reason, TUU may be a useful option for patients with a proximal ureteral stricture located near the sacral margin in the context of a radiated, reoperative, or otherwise diseased pelvis.³⁰ Contraindications to TUU include history of urothelial carcinoma, genitourinary tuberculosis,

idiopathic retroperitoneal fibrosis, and nephrolithiasis because progression and/or recurrence of the causative condition can result in compromise of both renal units and subsequent renal failure. A rarely used alternative to TUU is transureteropyelostomy, which has a theoretic lower risk of recipient ureteral stricture, but with the additional risk of donor ureteral obstruction caused by kinking as it crosses the retroperitoneum.¹³

Iwaszko and colleagues³¹ (2010) reported a series of 63 patients who underwent TUU, only 10 of whom underwent the procedure for stricture. The most common early complication was urinary leakage from the anastomosis (9.5%). Of the 10 who underwent TUU for stricture, the location the stricture was only reported in 1 patient (midureter). The complication rate was significantly higher for patients undergoing TUU for malignancy (47.6%) rather than benign reasons (11.9%). Of the 56 patients with follow-up imaging, patency was maintained in 96.4%. After TUU, the development of urolithiasis was seen in 8 patients (12.7%), 3 of whom had a previous history of urolithiasis. Six of those patients required percutaneous nephrolithotomy and 1 patient underwent ureteroscopic stone extraction.

URETEROCALICOSTOMY

Ureterocalicostomy (UC) is typically used for proximal ureteral strictures involving the ureteropelvic junction with an intrarenal pelvis and/or scarring of the renal hilum, thus preventing a widely patent anastomosis between the renal pelvis and ureter (typically seen following failure of previous pyeloplasty). Although UC is best suited for massively hydronephrotic kidneys with thinned parenchyma, it remains feasible with normal parenchymal thickness when a lower pole partial nephrectomy is performed to expose to the lower pole caliceal epithelium. The ureterocalicostomy is recommended by some to be the operation of choice for proximal ureteral obstructions in children with a horseshoe kidney.³² It has also proved to be a valuable option for managing ureteral necrosis following renal transplantation in which the native ureter is anastomosed to the lower pole calyx.³³ We prefer this operation for salvage of failed robotic pyeloplasty (**Fig. 2**).

A flank incision with partial resection of the 11th or 12th rib provides excellent exposure for the retroperitoneal approach to UC. The kidney is completely mobilized and the hilum is exposed. The strictured portion of the ureteropelvic junction and proximal ureter is excised. The renal pelvis is closed with 4-0 absorbable sutures at the level of the renal sinus. The lower pole of the kidney is

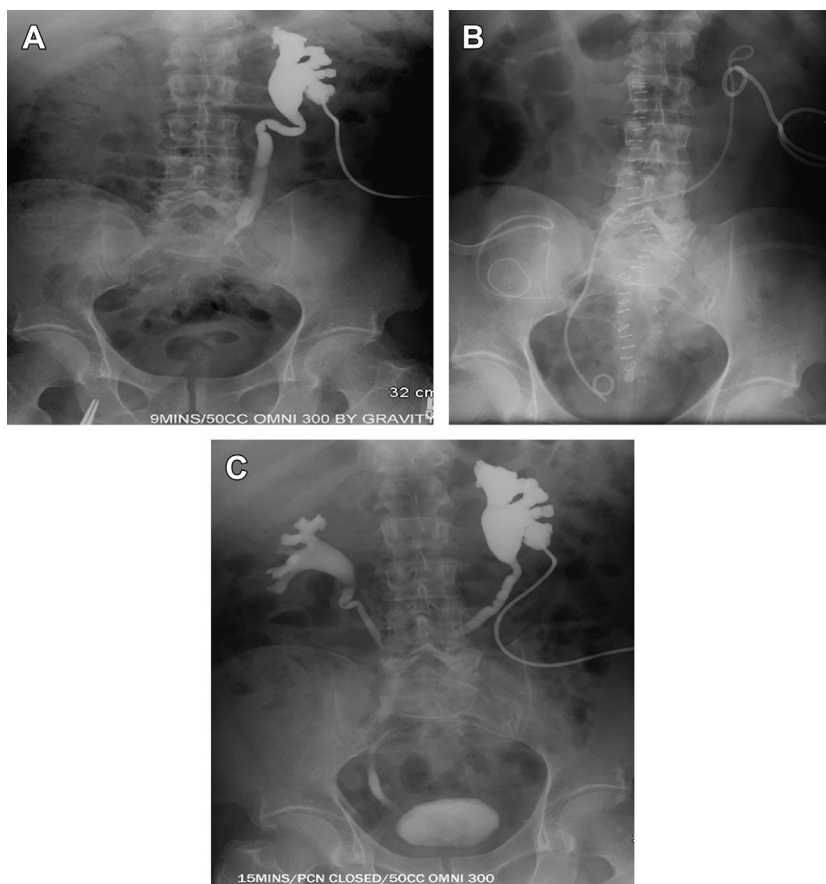


Fig. 1. Transureteroureterostomy. (A) Pyelogram showing left midureteral stricture. (B) Postoperative kidney-ureter-bladder with stent spanning from donor to recipient ureter. (C) Pyelogram after successful TUU.

widely amputated. The desire to preserve renal parenchyma by tunneling into the lower pole should be avoided because of the increased risk of stricture with this technique.³⁴ Preservation of a flap of renal capsule during the amputation process may allow closure of the capsule following the anastomosis, but this is not necessary and has been postulated to increase the risk of postoperative anastomotic stricture.^{24,35–37}

The renal artery may be clamped to minimize bleeding and improve visibility during anastomotic suture placement. As an alternative, local ischemia with a Penrose drain secured around the lower pole, suture ligation of the parenchymal surface, and/or argon beam coagulation may be used to limit global renal ischemia and the potential for renal artery thrombosis.³⁴

After amputation of the lower pole, the spatulated ureter is sutured to the lower pole calyx using 5-0 absorbable interrupted sutures. If anastomotic tension is present, downward nephropexy from the inferior aspect of the kidney to the psoas muscle or quadratus lumborum with 2-0 nonabsorbable

suture can be performed.^{24,31,38} Technical nuances of UC include vesicocalicostomy using a Boari flap and ileocalicostomy using an ileal ureter.^{39,40}

Only a few large series of UC exist in the literature. Osman and colleagues³⁶ (2011) reported a case series of 22 patients who underwent UC. The investigators reported complete cure in 12 patients, improvement in 4, no change in 2, and failure in 4. Of the patients who failed, 2 underwent nephrectomy and 2 were managed with chronic double-J ureteral stents. One injury to the inferior vena cava and 1 colonic injury occurred among the 22 patients. Matlaga and colleagues³⁵ (2005) reported a series of 11 patients who underwent UC for strictures measuring 0.5 to 3 cm with a mean follow-up of 10.1 months (range 5–32 months). None of these patients showed recurrent obstruction as measured by intravenous urography or nuclear renography.

BLADDER FLAPS

Described by Van Hook⁴¹ in 1893 with human cadavers, Boari⁴² with canines in 1894, and with

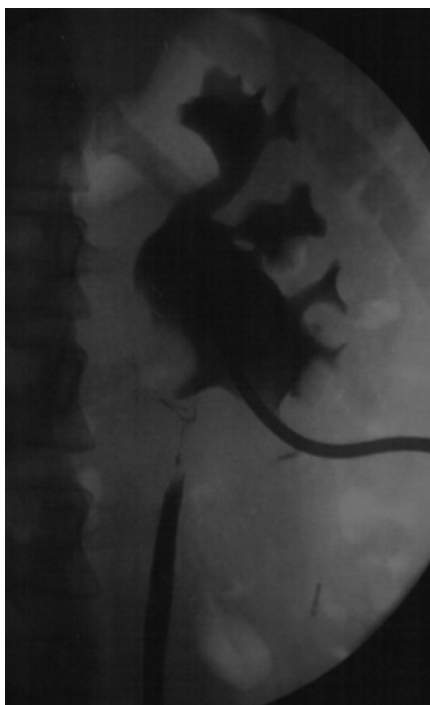


Fig. 2. Ureterocalicostomy. After 2 failed attempts with robotic pyeloplasty, this proximal ureteral stricture required ureterocalicostomy.

humans by Baidin⁴³ in 1930 and Ockerblad⁴⁴ in 1947, the use of bladder flaps continues to be an effective technique for complex ureteral reconstruction.⁴⁵ Although most investigators describe the Boari bladder flap (BBF) for mid ureteral strictures, Mauck and colleagues¹⁷ (2011) showed equivalent patency rates between BBF cases performed for ureteral strictures above and below the cephalad border of the sacroiliac joint. Thus, in well-selected patients, long Boari flaps can be created that reach high into the abdomen enabling near panureteral reconstruction.

The potential length of the BBF is directly related to the patient's preoperative bladder capacity, which can be assessed with cystometrogram, cystoscopy, voiding diary, and/or retrograde cystography.⁴⁶ Although some investigators suggest that a minimum bladder capacity of 400 mL is required for BBF, other reports suggest a minimum of only 150 mL.^{47,48} However, no studies have objectively measured preoperative and postoperative subjective and objective bladder function following BBF.

The BBF is performed by first releasing the bladder from its anterior attachments to the abdominal wall (obliterated umbilical arteries and urachus) and posteriorly from the peritoneum. Ligation and division of the contralateral superior vesical pedicle provides improved mobility, but

great care should be taken to avoid injury to the contralateral ureter.^{18,49,50} Ligation of the ipsilateral superior vesical pedicle risks compromise of the blood supply to the flap and should be avoided.

After bladder mobilization, the healthy ureter proximal to the stricture is mobilized and transected at the level of the stricture. The resulting ureteral defect is measured and an appropriately sized inverted U-shaped anterior cystotomy is made between stay sutures corresponding with the length of the defect. The length/width ratio of the bladder flap should be no more than 3:1 to preserve the vascular supply to the apex of the flap, and the base of the flap should be no less than 4 cm for the same reason.^{17,48,51} A spiral orientation provides additional length for small bladders or long flaps.⁵² Further length can be obtained by performing an adjunctive psoas hitch in a stepladder fashion between the flap and the psoas muscle or by making several transverse relaxing incisions on the flap.^{9,53,54} The tip of the flap is then anastomosed in a refluxing fashion to the healthy end of the ureter and the flap is tubularized over a stent in a running fashion with fine absorbable suture. The tubularization continues distally until the cystotomy is completely closed (**Fig. 3**). A suprapubic tube is unnecessary unless the cystotomy closure is tenuous.

Complications seen after a BBF may include recurrent stricture, seroma, ileus, bowel obstruction, urinary tract infection, urinary leak, bladder diverticulum, and irritative voiding symptoms.^{17,55} Success with the BBF is reported at greater than 90%.^{17,56}

DOWNWARD NEPHROPEXY

Laparoscopic or open downward nephropexy is sometimes necessary to relieve tension on the anastomosis following ureteral reconstruction. For proximal ureteral reconstruction, the downward nephropexy is often used in conjunction with other techniques to achieve an additional 4 to 10 cm of ureteral length, thus decreasing the need for bowel interposition and its attendant risks.^{17,57,58}

Downward nephropexy is performed by completely mobilizing the kidney from its attachments within the Gerota fascia. The division of the inferior adrenal artery or the left adrenal vein may also be performed, thus leaving the hilar vessels as the only remaining attachments and allowing the kidney to descend caudally.⁵⁷ The more caudal location is secured by suturing the renal capsule to either the quadratus lumborum or the psoas major muscle.

BOWEL INTERPOSITION GRAFTS

When proximal ureteral reconstruction using the native tissue is not feasible, tissue transfer

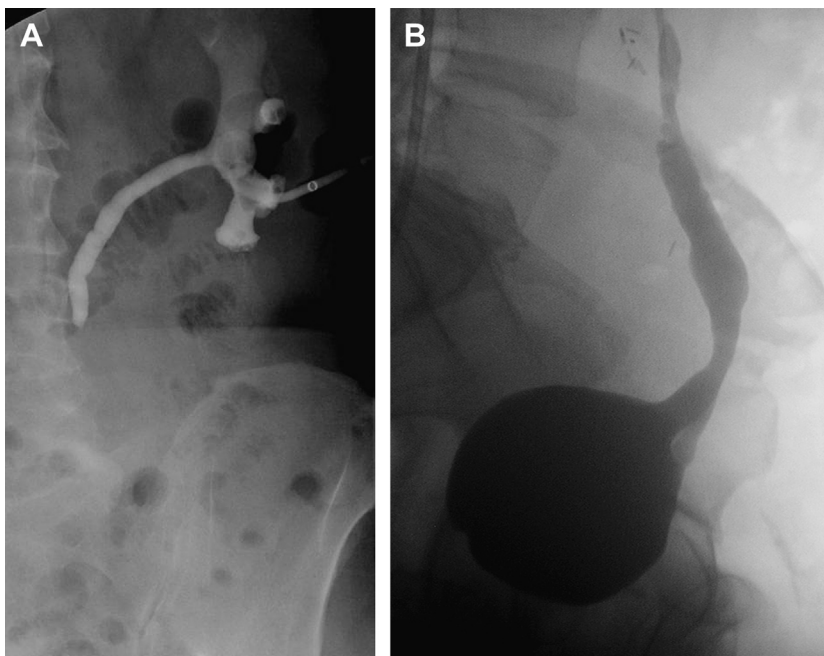


Fig. 3. Bladder flap. (A) Preoperative pyelogram with proximal ureteral stricture. (B) Following BBF, pyelography shows a widely patent reconstruction.

techniques are needed to restore ureteral continuity. Ileal ureter replacement is the preferred method for panureteral or long proximal segmental reconstruction. Additional indications for ileal ureter include a fibrotic, irradiated, and/or low-capacity bladder, which precludes safe construction of a BBF. For patients with severely decreased bladder compliance and/or capacity, an ileal ureter can be combined with bladder augmentation. Ileal ureter is also an option for bilateral ureteral substitution, allowing both renal units to drain through a single ileal segment into the bladder. Contraindications to ileal ureter include azotemia, hepatic dysfunction, inadequate length of usable bowel, untreated bladder outlet obstruction, and inflammatory bowel disease.^{59,60} Although abdominopelvic radiation is not a contraindication to ileal ureter, increased complication rates can be expected in radiated patients.⁶¹

The technique for performing an ileal ureter echoes that of the more commonly performed ileal conduit. After mobilizing the diseased ureter and dividing it at the proximal healthy end, the length of the ureteral defect is measured and an appropriate length of distal ileum is harvested 15 cm proximal to the ileocecal valve. Bowel continuity is restored and a window is created through the colonic mesentery to position the proximal anastomosis in the retroperitoneum.⁶² A refluxing end-to-end or end-to-side ureteroileal anastomosis has the lowest risk of stricture with little

risk for long-term renal damage when the ileal segment is oriented in an isoperistaltic position. A direct distal ileovesical anastomosis is also safe, simple, and imparts little risk for subsequent renal damage provided good bladder emptying is ensured (**Fig. 4**).⁶³

Contemporary series of ileal ureter substitution have shown excellent results with appropriately selected patients. Matlaga and colleagues⁶² (2003) published a series of 18 ileal ureter substitutions in 16 adults (preoperative creatinine 0.5–2 mg/dL) with a mean follow-up of 18.6 months that revealed no evidence of postoperative metabolic sequelae, renal insufficiency, or obstruction. Chung and colleagues⁵⁹ (2006) reported on 56 patients with 52 ileal ureters using an open refluxing ileovesical anastomosis with a mean follow-up of 6 years. Chronic kidney disease was observed in 3 patients who had preoperative azotemia. The largest series was published by Armatys and colleagues⁶¹ (2009) with 91 patients undergoing ileal ureter substitution (99 renal units) with a mean follow-up of 36 months. Anastomotic stricture occurred in 3.3% and fistula formation in 6.6%.

The ileal ureter may be complicated by bowel obstruction, mucus obstruction, stricture (ureter, ileal graft, or anastomosis), sepsis, secondary malignancy, hernias, deep venous thrombosis, pyelonephritis, recurrent urolithiasis, wound dehiscence, chronic kidney disease, severe dilatation of the ileal limb, and metabolic acidosis.^{59,64} Electrolytes

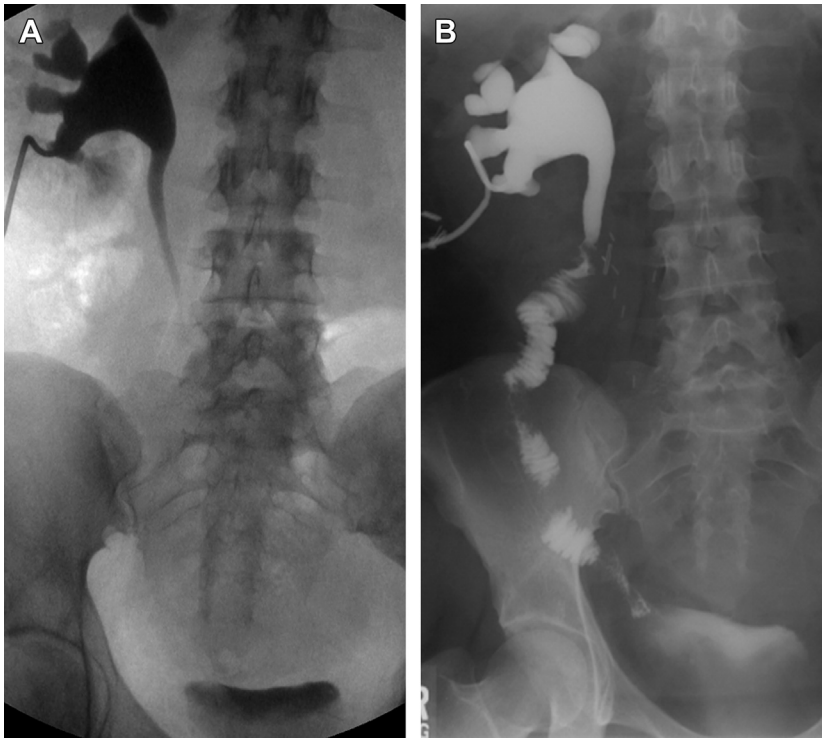


Fig. 4. Ileal ureter. (A) Preoperative pyelogram with proximal right ureteral stricture. (B) Antegrade pyeloureterogram following right ileal ureteral replacement.

should be assessed at least annually and any metabolic abnormalities treated. Mucus production may be managed with saline bladder irrigation or nightly intravesical acetylcysteine.⁶⁵ A small risk (0.8%) of secondary malignancy exists with placement of ileum into the urinary tract with a mean latency period of 18.5 years (range 12–32 years).^{66,67}

Melnikoff⁶⁸ reported the first ureteral substitution with appendix in 1912. The appendix is arguably an ideal bowel segment for ureteral replacement given its caliber, which is comparable with the ureter. However, the finite length of the appendix limits its use. Although most reports of ureteral substitution with the appendix have involved the right ureter, the left ureter has also been replaced. With normal peristalsis occurring from the appendiceal tip to the base, the appendix may be used in either isoperistaltic or antiperistaltic direction for ureteral replacement.^{69,70}

RECONFIGURED BOWEL INTERPOSITION GRAFTS

The use of reconfigured bowel to create a urinary conduit was described by Yang⁷¹ (1993) and shown in dogs by Monti and colleagues⁷² (1997). Compared with conventional ileal interposition, the benefits of reconfigured bowel segments include a

shorter length of bowel harvested, a smaller intestinal absorptive surface, and decreased mucus production. Both ileum and colon have been reconfigured and used as ureteral replacements in adults and children.^{69,73,74} However, the colon provides more length when detubularized compared with ileum because of its greater luminal diameter. Furthermore, the colon is conveniently located in the retroperitoneum near the ureter and away from the bony pelvis, and thus is unaffected by any previous pelvic radiation. This close proximity of the colon to the ureter allows for preservation of the marginal artery when harvesting the colonic segment. Indications for the use of colon in ureteral replacement include dense intraperitoneal adhesions or a shortage of usable ileum.

In this technique, a 3-cm to 4-cm segment of bowel is isolated, detubularized, and retubularized perpendicular to its original axis to form a long slender graft. Detubularization can be performed in either an antimesenteric or paramesenteric location. The latter provides an extended length of tubularized bowel with no mesenteric attachment, thus simplifying the creation of a submucosal antirefluxing anastomosis with the bladder. However, antimesenteric splitting optimizes blood supply to each end.⁷⁵ The detubularized graft is retubularized by closing it longitudinally over a

stent with a running 5-0 absorbable suture. The running suture is stopped before reaching the end of the tube, thus allowing a spatulated anastomosis. When the ureteral defect is too long for 1 reconfigured bowel segment, 2 segments may be used in tandem. Reconfigured colon is able to span a length of 8 to 10 cm for a single segment and 12 to 18 cm for a double segment. Although initial results with reconfigured bowel for ureteral reconstruction have been promising, larger studies with long-term follow-up are needed.⁷³⁻⁷⁷

RENAL AUTOTRANSPLANTATION

Renal autotransplantation is rarely required for complex ureteral strictures and should be used only when the previously discussed repairs are not possible or are contraindicated. Although initial reports indicated a high rate of perioperative renal loss, more contemporary series report excellent results from skilled renal transplant teams.^{10,78-82}

During the nephrectomy stage of renal autotransplantation, the length of the renal artery and vein should be maximized. Immediately following nephrectomy, the kidney is flushed with an ice-cold electrolyte solution and placed in ice slush for back bench preparation. If a laparoscopic donor nephrectomy is performed, a Gibson incision may be used for both the kidney extraction and the autotransplantation.^{83,84} The kidney is typically placed into the contralateral iliac fossa to maintain the vascular orientation, but this position may compromise the contralateral ureter.⁸⁵ For patients with a severely scarred renal pelvis and proximal ureteral stricture, autotransplantation may be combined with ureterocalicostomy (upper or lower pole) using the distally patent native ureter.⁸⁶

For patients with a history of nephrolithiasis, the use of a modified pyelovesicostomy may be advisable, in which the proximal ureter is split along its posterior aspect, including the ureteropelvic junction, to create at least a 2-cm opening in the renal pelvis.⁸⁷ A bladder flap is then created using a U-shaped incision with the base of the flap at least 4 to 5 cm wide. The bladder flap is laid on the split ureter and renal pelvis, effectively creating a large spatulation of both anastomotic ends. This large spatulation may decrease the risk of anastomotic stricture and allow future stone passage, thus limiting the need for renal/ureteral endoscopy.

NEPHRECTOMY

Nephrectomy is a viable, definitive treatment option for patients with complex proximal ureteral strictures in the presence of a healthy contralateral

renal unit. It is best suited for patients with long proximal or panureteral strictures who are unfit or unwilling to undergo one of the complex procedures listed earlier or for patients with severely compromised ipsilateral renal function (<20% differential function).

FUTURE DIRECTIONS

Drawing on the excellent results obtained with oral mucosal graft urethroplasty, several case series of oral mucosal graft ureteroplasty have been reported.⁸⁸⁻⁹⁰ The oral mucosal grafts may be used with either an onlay or tubular technique, commonly with incorporation of an omental wrapping to support the graft.⁹¹ These preliminary reports show the feasibility of this technique, but larger studies are needed.

Although numerous attempts have been made to identify the ideal material for ureteral substitution (**Box 3**), most modern efforts have focused on biologic materials. When engineering a synthetic biologic material for ureteral replacement, a tubular acellular scaffold is often created to mimic the extracellular matrix. Seeding this

Box 3 Materials studied for ureteral replacement
Poly (L)-lactic acid
Autologous external jugular vein
Dermal fibroblast tubes
Human amniotic membrane
Freeze-dried arteries
Bovine dermis
Allogenic human dura mater
Porcine small intestine submucosa
Silicone-polytetrafluoroethylene-bonded tube
Polytetrafluoroethylene tube
Omentocutaneous tubularized flaps
Tubularized grafts of bladder mucosa
Tubularized collagen sponge
Polyvinyl tube
Silicone tube
Dacron tube
Self-pumping synthetic ureteral prosthesis
Dimethylpolysiloxane with polyethylene glycol terephthalate
Partial-thickness tubularized skin graft
Fallopian tube

scaffold with urothelial and smooth muscle cells before surgical implantation has yielded tissues resembling normal urothelium and smooth muscle of the native ureter.⁹² The results of ureteral replacement with synthetic biologic materials are promising and further research is necessary before mainstream application of these methods. Even with advances in tissue engineering, the integral principles for reconstruction of a proximal ureteral stricture remain the same.

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Tips for Successful Open Surgical Reconstruction of Posterior Urethral Disruption Injuries

Joel Gelman, MD

KEYWORDS

- Posterior urethral disruption • Posterior urethroplasty • Pelvic fracture urethral distraction defect
- Urethral stricture • Urethral reconstruction

KEY POINTS

- After suprapubic tube placement, delayed open urethral reconstruction with excision and primary anastomosis via a perineal approach is the standard of care for the initial treatment of pelvic fracture urethral disruption injuries and treatment after failed endoscopic realignment.
- Before urethroplasty, accurate assessment of the defect is reliably obtained with a retrograde urethrogram and simultaneous antegrade cystourethrogram with contrast instillation through the tip of the scope positioned in the prostatic urethra.
- Vascular testing before urethral reconstruction may identify patients who are at risk for ischemic anterior urethral stenosis and who may benefit from penile revascularization before posterior urethroplasty.
- When performed using the proper technique, posterior urethroplasty offers a high success rate and a low complication rate.

INTRODUCTION: NATURE OF THE PROBLEM

Pelvic fracture trauma in males, often secondary to motor vehicle trauma or pelvic crush injuries, can be associated with injuries to the posterior urethra, especially where there is pubic symphysis diastasis or there are displaced inferomedial pubic bone fractures.¹ When the pelvis is fractured, the patient is often found to have blood at the urethral meatus. Additional symptoms and signs of urethral injury include bladder distension, inability to void, perineal hematoma, and possibly a high riding prostate on digital rectal examination.

A retrograde urethrogram (RUG) is indicated when a urethral injury is suspected and typically

shows extravasation as a result of a partial tear, or more often, a complete disruption. The term prostatomembranous disruption is often used to describe these injuries, and this terminology suggests that the transection occurs at the junction of the prostatic and membranous portions of the posterior urethra. However, more recent studies, including an autopsy review of male patients who sustained pelvic fracture-related urethral injuries and died of associated multiple trauma, revealed that the injuries are generally bulbomembranous and distal to the urogenital diaphragm.² There can be proximal or distal extension, but the injury generally remains distal to the verumontanum of the prostate. Continence after repair is maintained

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primarily by the proximal bladder neck. However, in many patients, there is also a significant rhabdosphincter contribution, as shown by video urodynamic testing after reconstruction.³

The standard management approach is suprapubic tube placement and delayed posterior urethral reconstruction. Alternatively, primary realignment can be performed, which is discussed by Wessels and colleagues, elsewhere in this issue. Should this option fail, the definitive treatment is then delayed posterior urethroplasty with excision and primary anastomosis via a perineal approach.

SURGICAL TECHNIQUE: PREOPERATIVE PLANNING

3-Month Delay

We wait 3 months from the time of injury or catheter removal in cases of failed primary realignment before performing urethroplasty, to allow time for the initial extravasation to heal, hematoma to resolve, and the extent of the injury to become clearly defined. It has been shown that after manipulation, several months of urethral rest is required for before anterior urethral strictures become clearly defined.⁴ When there is a pelvic fracture–associated injury to the posterior urethra, initial imaging reveals extravasation, whereas imaging 3 months after injury typically confirms no extravasation and clear delineation of the location and length of the defect. Recent publications indicate that the delay is often a minimum of 3 to 6 months. However, the interval between initial injury and urethroplasty can exceed 1 year when there are associated injuries.^{5–9} A recently presented abstract indicated that urethral reconstruction less than 6 weeks after the injury may be associated with results similar to when there is a delay of 3 or more months.¹⁰ However, there are no recent publications suggesting that a delay of less than 3 months is appropriate, and the current delay of no less than 3 months is the current published minimum period of urethral rest.

Suprapubic Urinary Diversion

Suprapubic tube urinary diversion always precedes urethroplasty. The ideal suprapubic tube is no less than 16 French, midline, and 2 finger-breadths above the pubic symphysis. However, patients are often initially managed with tubes that are far lateral to the midline or just above the symphysis. In some cases, very small caliber pigtail catheters are placed (**Fig. 1**). When patients are referred for posterior urethral reconstruction, and have tubes of inadequate caliber or if the tube is not in the ideal position, it is our preference to percutaneously place a new 16-Fr tube. This

procedure is generally performed as soon as possible when the caliber is small, and no less than 1 month before urethroplasty so there will be an established stable tract at the time of surgery. Small caliber pigtail catheters are especially prone to encrustation and urinary retention. Moreover, catheters placed just above the symphysis are more uncomfortable than catheters placed in a higher position away from the bone. The main benefit of having the suprapubic tube midline well above the symphysis with an established tract is that this facilitates the surgery and prevents the need for a temporary vesicostomy. During posterior urethroplasty with the patient in the lithotomy position, after perineal exposure is achieved and the urethra is transected, a metal sound is generally advanced through the established tract, and perineal dissection proceeds toward the tip of the sound until the sound can be seen and advanced into the perineum. When the caliber of the tract is inadequate, sounds do not advance without dilation at the time of the surgery. This situation can be associated with bleeding and compromise of the tract. When the tube is just above the bone, a very acute angle is needed to advance the sound through the bladder neck. Moreover, when the tract is lateral to the midline, the rigid sound cannot be reliably advanced medially toward the midline bladder neck and then distally along the posterior urethra. One option is to create a temporary vesicostomy. However, this procedure adds considerable time and morbidity to the reconstructive surgery and therefore this is not our preference.

PREOPERATIVE URETHRAL EVALUATION: CYSTOSCOPY

Before definitive urethral reconstruction, urethroscopy, antegrade cystoscopy, and a simultaneous antegrade cystourethrogram and RUG together provide a definitive diagnosis of the length and location of the defect. One common imaging technique is for the bladder to be filled with contrast by gravity through the suprapubic tube and for an RUG to be performed as the patient is asked to perform the Valsalva maneuver and attempt to void. As the patient attempts to void, if the bladder neck opens, there is filling of the posterior urethra proximal to the obliteration, and the length of the defect is determined (**Fig. 2A**). However, in many cases, the patient cannot relax to void when the urethra is obliterated and contrast is being injected through the penis. When the bladder neck is intact, the appearance is as shown in **Fig. 2B**. The distance between the bladder and the distal end of the defect is not the length of

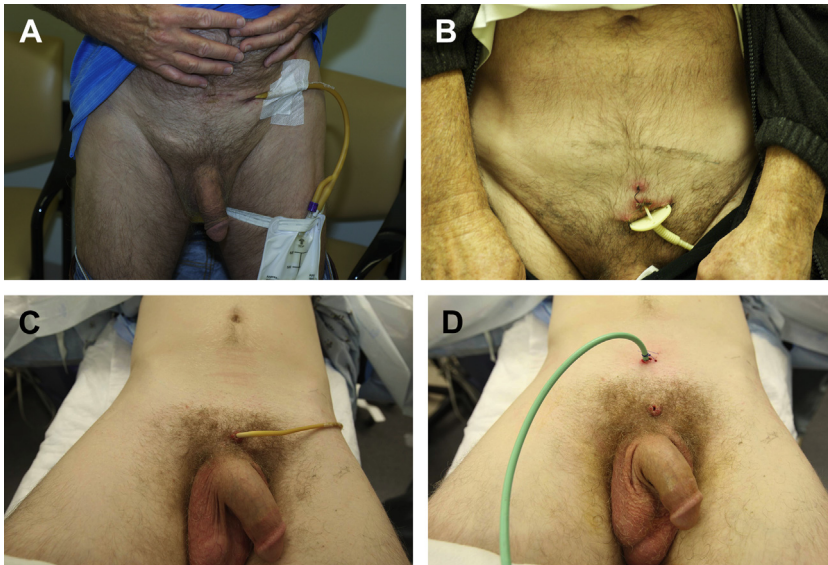


Fig. 1. (A) Laterally placed suprapubic tube. (B) Small pigtail catheter of inadequate caliber. (C) Suprapubic tube placed below the ideal location. (D) Suprapubic tube repositioned midline 2 finger breaths above the midline pubic symphysis.

the distraction defect, because the prostatic urethra is not visualized. In a recent study in which the goal was to determine if the type of urethroplasty could be predicted based on certain features from the preoperative imaging, 38% of the 100 study patients evaluated with a Valsalva cystourethrogram and RUG were excluded because there was no visualization of the urethra below the bladder neck.⁴

Our preferred approach is to first perform antegrade cystoscopy with the patient prepared and draped in the oblique position after a 35 × 43 cm (14 × 17 inch) scout film is obtained to confirm proper position and penetration. Some patients develop bladder calculi, and when identified, the stones can be removed before urethroplasty. The bladder neck is then inspected for coaptation. An open bladder neck at rest suggests that there may be an increased incidence of incontinence

after urethral reconstruction. Iselin and Webster identified 15 patients who sustained pelvic fracture urethral injuries and had an open bladder neck at rest.¹¹ Six were continent and 8 were incontinent after urethroplasty. However, MacDiarmid and colleagues¹² identified 4 patients who had an open bladder neck at rest, and all of these patients were continent after surgery. Although some surgeons occasionally perform bladder neck reconstruction at the time of posterior urethroplasty,¹³ most reconstructive urologists do not perform simultaneous bladder neck surgery, given the observation that an open bladder neck at rest does not reliably predict postoperative incontinence. When we observe an open bladder neck at rest, the patient is counseled that there may be an increased incidence of postoperative incontinence, but this finding does not influence our management.

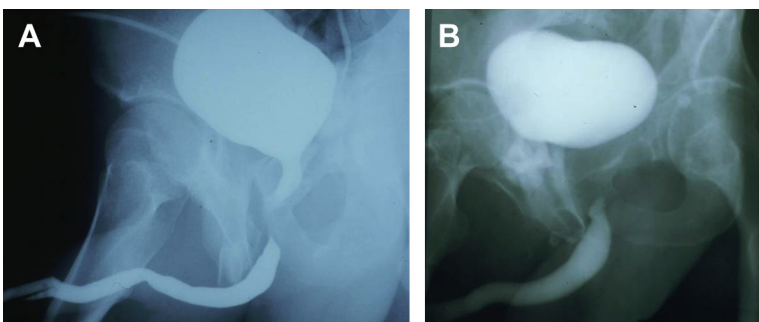


Fig. 2. (A) After the bladder is filled with contrast through the suprapubic tube, an RUG is performed as the patient is asked to attempt to void. If the bladder neck opens, contrast fills the prostatic urethra, and the membranous urethral defect is seen. (B) When the bladder neck does not open, the length of the defect cannot be determined accurately.

PREOPERATIVE URETHRAL EVALUATION: URETHRAL IMAGING

Once the scope is advanced through the bladder neck, the location of the proximal aspect of the injury is noted, and this is almost always distal to the verumontanum of the prostate within the membranous urethra. With the tip of the scope at the level of the obliteration, full-strength contrast is injected, which then back fills the posterior urethra and bladder. Simultaneously, an RUG is performed. Our preferred technique for performing an RUG is to place a gauze around the coronal sulcus to place the penis on stretch, and inject contrast through a cone-shaped Taylor adaptor (Cook Urological Incorporated, Spencer, IN, USA) connected to a 60-mL syringe filled with full-strength contrast (**Fig. 3**). Many published textbooks advocate the advancement of a catheter into the fossa navicularis and inflation of the balloon with 1 to 3 mL of contrast for form a seal. However, the balloon caliber of catheters of several different sizes when inflated with only 2 mL of fluid or air is approximately 59 French, and the normal caliber of the adult anterior urethra is approximately 30 French, except at the level of the urethral meatus and fossa navicularis, where the caliber is approximately 24 French (**Fig. 4A**). Therefore, the balloon dilates the normal distal anterior urethra, which can be associated with considerable pain and even stricture disease of the fossa navicularis. We have seen patients referred for strictures initially limited to the bulbar urethra who then developed narrow caliber fossa strictures after undergoing painful urethral imaging when the technique included balloon inflation within the fossa navicularis (see **Fig. 4B**).

Simultaneous antegrade and retrograde imaging and endoscopy performed with proper technique clearly defines the length and location of the defect. Other imaging modalities that can be used include magnetic resonance imaging and ultrasonography.¹⁴ However, we have never found an indication to perform these additional

tests. Fluoroscopy offers the advantage of dynamic real-time imaging. However, disadvantages include a reduced field of view and decreased resolution compared with conventional radiographs. We prefer flat plate imaging using digital cassettes that can be digitized and stored electronically and also printed on 14 × 17 film. Although magnification and positioning can influence the scale, we have observed that the length of the obliteration measured directly on the film accurately corresponds to the length of the defect at the time of surgery. Most defects are 1 to 3 cm in length and within the membranous urethra, with possible extension into the most proximal bulbar urethra. Although pelvic fracture trauma typically injures the posterior urethra, if there is also straddle trauma at the time of the pelvic fracture, the injury can be to the bulbar urethra. The specific location of the injury can influence the management. For example, a man who sustained pelvic fracture trauma during a race car accident was found to have significant extravasation on an RUG on the day of the injury and was managed with a laterally placed suprapubic tube. Delayed imaging and antegrade cystoscopy confirmed a proximal bulbar urethral defect and a normal membranous urethra (**Fig. 5**). Although both traumatic proximal bulbar and membranous disruptions are managed with excision and primary anastomosis, bulbar urethroplasty does not require antegrade access to facilitate identification of the patent proximal segment. If the injury were membranous, then a new midline suprapubic tube would have been placed to facilitate subsequent antegrade access to the proximal segment at the time of posterior urethroplasty. However, because antegrade access is not required for bulbar urethroplasty, the placement of a new midline tube was not required.

PREOPERATIVE VASCULAR EVALUATION

The anterior urethra has a dual blood supply, with an additional minor contribution provided by

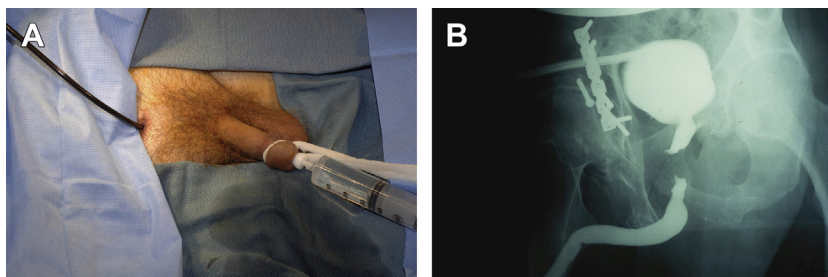


Fig. 3. (A) A RUG is performed as contrast is simultaneously injected into the posterior urethra through the flexible cystoscope, with the tip in the distal prostatic urethra. (B) Imaging accurately shows the length and location of the defect.

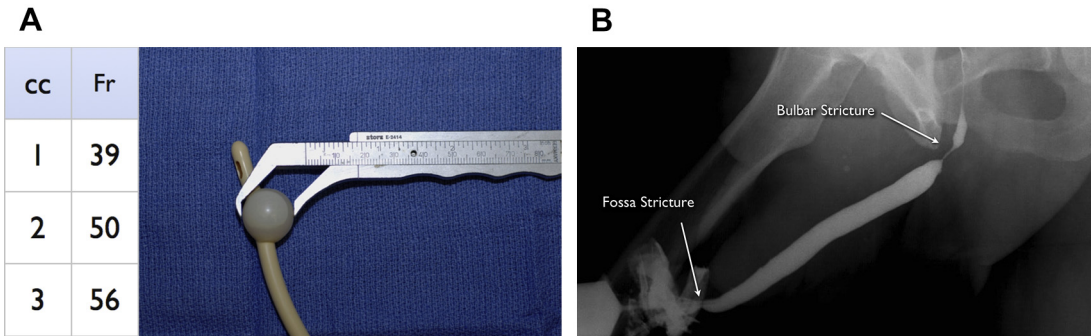


Fig. 4. (A) Catheter balloon inflation with only 1 to 3 cm³ of air or fluid is associated with balloon inflation well beyond the normal caliber of the normal fossa navicularis. (B) Repeat RUG showing in addition to the previously seen bulbar stricture, a new fossa navicularis stricture, which developed after an RUG was performed using fossa balloon inflation technique.

perforating vessels between the corpora cavernosa and the corpus spongiosum. The bulbar arteries enter the corpus spongiosum at the level of the most proximal bulbar urethra and provide antegrade flow to the corpus spongiosum of the anterior urethra. In addition, the dorsal arteries course within the neurovascular strictures along the dorsal aspect of the penis superficial to the corporal bodies and supply the glans penis, which is the distal expansion of the corpus spongiosum. This anatomy provides a secondary blood supply to the anterior urethra as the blood courses in retrograde fashion along the corpus spongiosum. When the urethra is completely transected at the departure of the anterior urethra, any patent bulbar arteries are ligated or cauterized. The anterior urethra then survives as a flap based on the retrograde dorsal artery contribution in addition to perforating vessels. Although results are unpublished, it has been observed by several reconstructive urologists that in rare cases, long-segment bulbar strictures developed as

an ischemic complication of posterior urethroplasty. The mechanism of the ischemic stenosis was presumed to be compromise of the bulbar artery supply during surgery in patients who suffered perineal trauma that compromised dorsal artery supply. We have observed cases of ischemic stenosis in patients with hypospadias who developed discreet bulbar strictures and were treated with a urethral stent.¹⁵ Before stent placement, these patients were noted on urethroscopy to have a normal caliber anterior urethra distal to the bulbar stricture. After stent placement, they developed severe panurethral disease. This finding makes sense anatomically because hypospadias and corrective surgery are associated with a compromise of the corpus spongiosum distally and the associated retrograde blood supply to the more proximal anterior urethra. These patients were likely bulbar dependent, and stent expansion compromised the antegrade bulbar artery flow distal to the stent. Therefore, in addition to antegrade cystoscopy and contrast imaging, we perform a preoperative vascular evaluation to identify patients who have severe arterial inflow compromise to both dorsal arteries, and perform penile revascularization before urethral reconstruction in selected cases. Penile revascularization provides a microvascular anastomosis of the inferior epigastric artery to the dorsal artery of the penis (**Fig. 6**).

Erectile dysfunction and pudendal vascular injuries are highly associated with pelvic fracture urethral disruptions. In a study by Shenfeld and colleagues,¹⁶ 25 patients who sustained traumatic posterior urethral disruptions were evaluated with nocturnal penile tumescence testing. Eighteen patients (72%) were found to have erectile dysfunction, and these patients underwent a penile duplex with pharmacologic erection that revealed arterial inflow impairment in 5 of 18



Fig. 5. Simultaneous antegrade and retrograde urethral imaging showing a bulbar urethral obliteration, further confirmed with antegrade cystoscopy.

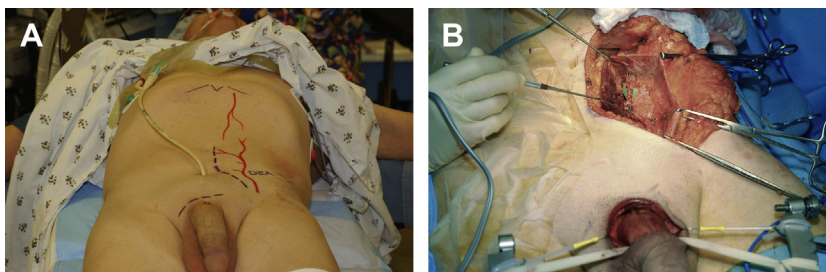


Fig. 6. Inferior epigastric artery to dorsal artery penile revascularization, shown after skin marking (A) and during surgery (B).

patients. The remaining patients were considered to have a neurogenic cause of their erectile dysfunction. Davies and colleagues¹⁷ performed a penile duplex testing on 56 men who sustained posterior urethral disruptions, and identified 25 men with vascular compromise. These patients underwent arteriogram. Twenty-one had reconstitution of 1 or both pudendals, and 4 did not. These 4 patients underwent revascularization before urethral reconstruction, and no patient developed ischemic stenosis after surgery. A limitation of this study is that it is not known if any of these patients would have developed stenosis if reconstruction had been performed without prior revascularization. This is an area of controversy. However, we believe that vascular testing and revascularization in selected cases may be justified based on the anatomic principals and the available data. Moreover, revascularization often successfully treats the erectile dysfunction associated with pelvic fracture injuries.¹⁸

POSTERIOR URETHRAL RECONSTRUCTION: PREPARATION AND PATIENT POSITIONING

Before surgery, which we generally perform approximately 3 months after injury, patients are placed in high lithotomy during a physical examination to assess hip flexion and ability to tolerate this position. Some patients may have unresolved back or other orthopedic problems, which may then be exacerbated by prolonged lithotomy positioning. In our series of 85 patients, the longest delay was 19 months. This patient had severe compromise of hip flexion, which persisted more than 12 months after the injury. With ongoing physical therapy, mobility returned to normal, and positioning was safely accomplished without compromise. A urine culture is sent the week before surgery. The specimen is obtained by clamping the suprapubic tube, and then unclamping the tube 20 minutes later over a specimen container. The sample is then obtained directly from the suprapubic tube and not the drainage

bag. Any mixed growth is separately cultured. Patients are admitted the day before surgery for dual coverage antibiotics. Our protocol is to administer piperacillin/tazobactam and tobramycin, but adjust the antibiotics if indicated based on the culture result. No patient has suffered the complication of a perineal infection, which can be associated with urethral compromise and stricture development.

Although some reconstructive urologists prefer a low lithotomy position, in many centers and at our institution, exaggerated lithotomy positioning is preferred. This position can be associated with severe complications, including neuropraxia, compartment syndrome, and rhabdomyolysis.^{19–21} Neuropraxia is usually not permanent. Sensory deficits are more common than motor impairment, and the risk of a positioning complication is related to the time in lithotomy. One form of exaggerated lithotomy, often used for perineal prostatectomy, places hips under considerable flexion so that the thighs are parallel to the back and the floor. In a study by Holzbeierlein and colleagues,²² of 111 men who underwent a radical perineal prostatectomy in this extreme lithotomy position with a mean duration of less than 3 hours, 23 (21%) suffered a positioning complication. Of these 23 patients, 17 had symptoms at the time of discharge, and 6 required physical therapy support for ambulation.

We use a Skytron Custom 6000 table modified by Jordan to offer an electronic pelvic tilt mechanism to cradle the pelvis as an alternative to raising the buttocks and placing a beanbag support (Fig. 7A). In addition, stirrups are modified to provide additional extension so that hip and knee flexion is reduced. Foam padding is placed along the dorsal feet and anterior legs to evenly distribute the pressure (see Fig. 7B). We previously used gel pads, and found a significantly reduced incidence of temporary (24-hour to 48-hour) dorsal foot numbness after a change of the use of the softer foam. Extreme flexion of the hips and knees is avoided, and the boots

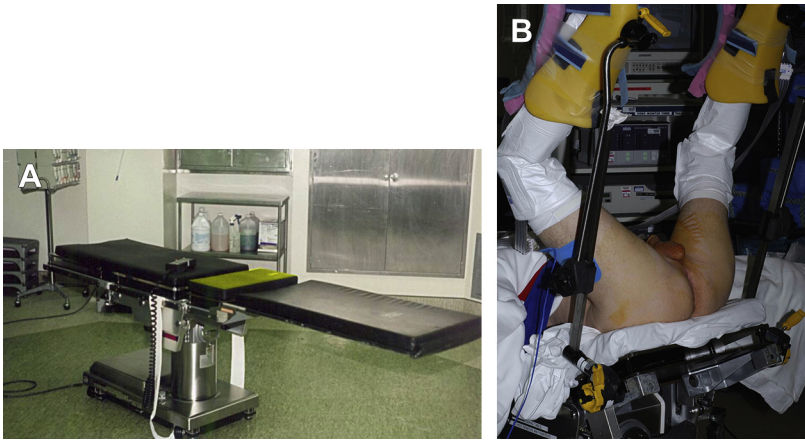


Fig. 7. (A) Modified Skytron Custom 6000 surgical table with pelvic tilt mechanism (highlighted in yellow), (B) Patient placed in exaggerated lithotomy position.

are tilted so that there is no pressure on the calves.

POSTERIOR URETHRAL RECONSTRUCTION: SURGICAL TECHNIQUE

Exposure

A midline perineal incision is 1 option. We prefer an inverted Y-shaped λ incision to obtain generous exposure (**Fig. 8A**). This incision is carried medial to the ischial tuberosities posteriorly and along the median scrotal raphe. Dissection then proceeds sharply through the subcutaneous fat longitudinally along the midline until the bulbospongiosus muscle is encountered. The Jordan-Simpson perineal retractor is used to facilitate exposure as shown in **Fig. 8B**. Although other retractors are commercially available such as the Lone Star retractor, advantages of the Jordan retractor include fixation of the ring and the ability to use a variety of different specialized blades in

addition to the hooks used in the Lone Star system. In addition, tilt ratchets facilitate lateral retraction to facilitate exposure. The bulbospongiosus muscle is then divided and retracted laterally to expose the bulb. The bulb is detached from the perineal body, and we find that the use of a bipolar cautery facilitates this dissection and maintains hemostasis to the extent that suction is seldom required. The urethra is then circumferentially mobilized from the penoscrotal junction distally to the departure of the anterior urethra proximally (see **Fig. 8C**). This is performed sharply without the use of right angle clamps, which can tear the corpus spongiosum. The bulbar arteries are transected and cauterized if patent.

Several recent articles have described bulbar artery-sparing anastomotic anterior urethroplasty.^{23,24} Although the use of artery-sparing surgery during posterior urethral reconstruction has not been published, a recent abstract²⁵ described the successful use of this

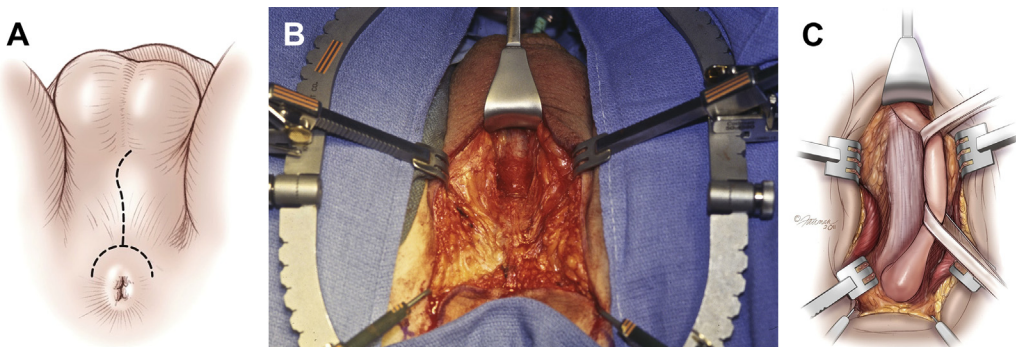


Fig. 8. (A) λ Incision with the patient in the exaggerated lithotomy position. (B) Jordan-Simpson perineal retractor is used to facilitate exposure of the corpus spongiosum. (C) The corpus spongiosum is circumferentially mobilized along the bulbar urethra.

technique in 9 patients. Intraoperative ultrasonography was performed, and the artery with the strongest signal was preserved. No patient developed a recurrent stricture with a mean follow-up of 10 months. This finding may possibly represent a future modification of operative technique.

Proximal Exposure and Scar Excision

After transection of the urethra, unless preoperative imaging suggests very short segment obliteration, we routinely separate the corporal bodies at the level of the triangular ligament and retract them laterally to improve proximal exposure and facilitate excision of the scar tissue, which is generally whitish and firm.

The suprapubic tube is then removed and a curved metal sound is advanced through the established tract into the bladder and then through the bladder neck, guided by feel, until the impulse of the tip of the sound can be palpated in the

perineum as the sound is manipulated. This technique guides the dissection in the appropriate direction toward the patent proximal urethra. One option is to advance a Van Buren sound. Although these instruments are often readily available and familiar to most urologists, the fact that the instrument is curved only at the tip and tapered to a more pointed tip relative to the shaft of the instrument renders these instruments poorly suited to use in posterior urethroplasty, especially when an exaggerated lithotomy position is used. However, the semicircular Haygrove sound is designed to best follow the path from the suprapubic access to the membranous urethra (**Fig. 9A, B**). The caliber is not greater than 16 to 18 Fr, and therefore, no tract dilation is required if the indwelling suprapubic tube was 16 Fr. In addition, the tip is curved and smooth. However, in some cases, the tip of the sound may not be palpable. This situation may be because of the presence of very dense scar or malposition of the sound. If dissection proceeds in the wrong direction, what is

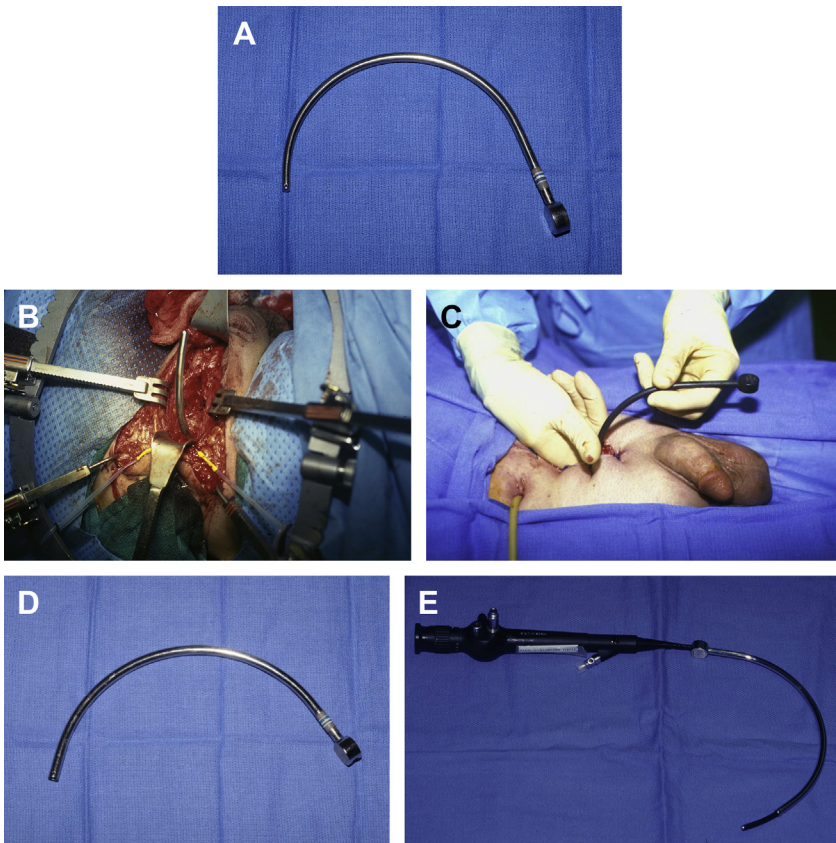


Fig. 9. (A) Solid Haygrove sound. (B) After dissection of the obliterative scar, the tip of the sound (placed through the suprapubic tract) can then be advanced through the patent proximal urethra into the perineum. (C) Temporary vesicostomy in a patient with a laterally placed suprapubic tube. (D) Gelman visualizing posterior urethral sound. (E) Flexible scope advanced through the hollow visualizing sound.

entered may be the bladder or the posterior urethra proximal to the distal aspect of the patent urethra. This situation may lead to postoperative incontinence or restenosis. The limitation of a solid sound is that it is guided blindly. If a flexible cystoscope is used, the scope can be guided under direct vision. However, because the active scope deflection is limited only to the tip of the scope, it may be difficult to advance the tip of the scope to the proper position, especially when the patient is in high lithotomy and the surgeon is positioned at the level of the perineum. To prevent the possibility of false passages, some surgeons perform rigid antegrade cystoscopy before the patient is prepared and draped in the exaggerated lithotomy position, advance the scope through the bladder neck and prostatic urethra, then palpate the perineum to determine if the tip of the scope is palpable or not.²⁶ When the tip of the scope is not palpable, or if the suprapubic tube is laterally located, a temporary vesicostomy is created before lithotomy positioning and then taken down after the completion of the repair (see **Fig. 9C**). It was determined that the creation of the vesicostomy allows the surgeon to palpably identify the bladder neck before instrumentation of the posterior urethra, and that this maneuver eliminates the occurrence of false passages and the misanastomosis of the anterior urethra to sites other than the apical prostatic urethra. This maneuver adds considerable time and morbidity to the surgery.

For this reason, we prefer to always proceed with a midline suprapubic tube, even if this requires placement of a new tube no less than 1 month before urethroplasty to allow time for the tract to mature, and use a new visualizing sound (Gelman Urethral Sound, CS Surgical) (see **Fig. 9D**). This sound has a contour similar to the Haygrove sound, but is hollow, allowing a flexible cystoscope to be advanced through the sound (see **Fig. 9E**). The tip of the sound or the tip of the cystoscope can then be directed to the obliteration under direct vision. An additional advantage is that the light from the scope can be seen to further guide the dissection. Before the development of the visualizing sound, 2 of 9 patients required a temporary vesicostomy at the time of reconstruction. Subsequently, 76 patients (ages 4–77 years) underwent reconstruction, (including 6 pediatric patients, and 14 patients who had unsuccessful procedures before referral), and 0 of 76 patients required a temporary vesicostomy. In every case, the sound could be directed to the proper position under direct vision. It is our experience that the visualizing posterior urethral sound greatly facilitates the reliable identification and

dissection of the proximal segment during posterior urethral reconstruction. With the use of this device, the open dissection can be limited to the perineal exploration, even in pediatric and difficult cases. One disadvantage of the sound is that the outside diameter is greater than the outside diameter of the solid Haygrove sound, and the solid sound can be manipulated more easily. Therefore, we continue to use the solid sound when the tip can be readily palpated in the perineum. Although the larger-diameter hollow sound does not advance as easily though the suprapubic tract when 16-Fr to 18-Fr indwelling tubes are used before surgery, the tip of the flexible cystoscope can be first advanced into the bladder, and the sound can then be advanced over the scope using the scope as the equivalent of a guide wire.

The most complex portion of posterior urethral reconstruction is the proximal exposure and dissection after transection of the urethra. One option is to sharply incise scar tissue, advance a nasal speculum through the scar, and place J-shaped sutures through the speculum to initiate the anastomosis.²⁷ It is our preference to excise the scar tissue until normal healthy tissue is encountered. Supple tissue more readily everts, bringing the mucosa forward from deep within the pelvis during the placement of the first several sutures, and this facilitates the placement of subsequent sutures. Our objective is to achieve the proximal preplacement of 10 to 12 3-0 absorbable monofilament sutures. We alternate using violet PDS and clear Monocryl to help maintain orientation at the time of the completion of the anastomosis.

Infrapubectomy

In cases in which the scar is especially dense and the defect is long, it is possible that the tip of the sound is not palpable, and the light of the cystoscope is not seen even if it is confirmed using the visualizing sound that the tip of the sound and scope are in the appropriate position at the distal aspect of the patent posterior urethra. In these cases, scar tissue just below the midline symphysis is excised sharply in a 1-cm-diameter to 2-cm-diameter area. As the scar is excised, the dissection extends deep into the pelvis, and it is in these cases in particular that infrapubectomy is often required. After the separation of the corporal bodies at the level of the triangular ligament and lateral retraction, the dorsal vein is then mobilized and ligated, exposing the midline symphysis pubis. Periosteal elevators are then used to sweep the medial crura laterally and free the undersurface of the bone from adherent tissue. Kerrison rongeurs provide controlled bone

removal, which widens the exposure and facilitates further proximal dissection. Moreover, the separation of the corpora and infrapubectomy provide a more direct route for the urethra to course, and this facilitates a tension-free repair.

Additional Maneuvers

Some investigators have reported that in addition to distal mobilization, crural separation, and infrapubectomy, supracrural corporal rerouting was required to achieve an acceptable amount of tension in select cases.²⁸ This technique seems to be associated with a high rate of restenosis. In a recently published combined series of 142 cases, 4 underwent rerouting and 3 of these patients (75%) developed restenosis.⁹ Other surgeons never find supracrural rerouting to be a beneficial maneuver. It is often stated that the objective is a tension-free anastomosis. This procedure is not necessary because there is normally a certain amount of innate tension along the corpus spongiosum. For this reason, when the urethra is transected, there is generally some retraction of the distal segment. Our goal is not a tension-free anastomosis, but rather an anastomosis without unacceptable tension that would lead to tethering of the penis during erections or separation of the anastomosis. We have never encountered a case in which supracrural rerouting was required.

Another option in complex cases in which there is a large gap is a transpubic approach.^{29–31} We have never found this technique necessary, and more recent reports³² confirm that infrapubectomy generally provides adequate proximal exposure in complex cases. Moreover, tissue transfer with flaps or grafts has been reported as an option to bridge longer defects.²⁸ This procedure seems to have been performed mostly in older series, and recent reports do not support the use of or need for tissue transfer. It is fortunate that excision and primary anastomosis can reliably be achieved during posterior urethral reconstruction, given that tube flaps and grafts are generally associated with a high failure rate, and the tissues surrounding the membranous urethra deep within the pelvis proximal to the triangular ligament do not represent a suitable bed for graft spread fixation.

Anastomosis

Once the proximal sutures are placed along a widely patent proximal segment surrounded by pink healthy mucosa proximally, and flexible cystoscopy further confirms that the opening is distal to the verumontanum at the appropriate location, the distal segment is dorsally spatulated and calibrated using bougies à boule. The caliber

should be greater than 30 Fr. The anastomosis is then completed as a stenting catheter is placed. It is our preference to use a 14-Fr soft silicone catheter. A small TLS train is placed deep adjacent to the corpus spongiosum deep to the bulbospongiosus muscle, which is then reapproximated along the ventral midline, and a second flat 7-mm drain is placed superficial to the muscle. The incision is then closed in 2 layers with absorbable suture and a clear dressing is placed. No compressive dressing is required.

Postoperative Care

Our protocol is to maintain the stenting urethral catheter and the suprapubic tube urinary diversion for 3 weeks, and then perform a voiding cystourethrogram by removing the stenting catheter, filling the bladder with contrast by gravity installation, and then obtaining a film during urination. In the rare case of extravasation, a new stenting catheter is replaced and a repeat study is performed the next week. Other surgeons favor catheter removal without postoperative imaging.³³ In most cases, the force of stream is excellent, and the suprapubic tube is then removed. If the stream is not weak, the tube is plugged and the patient is instructed to unplug the tube at home if unable to urinate and to check residuals by unplugging the tube after micturition. One possible reason for voiding difficulty is neurogenic bladder dysfunction related to the initial injury, especially if there is associated back trauma. Several months after tube removal, flexible urethroscopy is performed to definitively confirm wide patency of the repair. Patients are then encouraged to have a baseline flow rate and postvoid residual assessment, and then to have this repeated annually. There is a lack of consensus regarding appropriate follow-up after surgery.

Outcomes

In our series of 85 patients, before referral, 17 underwent failed endoscopic treatment and 17 underwent failed open surgery. At the time of surgery, 19 patients underwent infrapubectomy, and no patient required supracrural rerouting. No patient required transfusion, and the only persistent neuropraxia was in 1 patient, who had persistent tingling of the toes, which resolved after several months. At the time of urethroscopy 4 months after surgery, 2 patients were noted to have medium caliber narrowing. One of these patients underwent dilation 2 years after surgery and the other was observed and never required treatment. This finding corresponds to a success rate of 97.6% success, defined as durable wide

patency of the repair and with no further treatment required.

Other series report a similar success rate for adults, adolescents, and children, and this indicates that a stricture recurrence after a properly performed posterior urethroplasty should be a rare event.^{32,34} Of the patients who presented to our center after failed surgery, the recurrence was often within days or weeks, suggesting that these were technical failures, likely because of inadequate scar excision with an anastomosis to a widely patent segment of proximal urethral mucosa. Further suggesting that technical inexperience of the surgeon is likely the most common cause of failure is the fact that these patients usually have a successful outcome with the same technique of excisional repair when the revision surgery is performed by a specialist in urethral reconstruction. Published studies from referral centers confirm that when open repair fails, excision and primary anastomosis still remains the procedure of choice and when properly performed, offers a high success rate.^{35,36} Delayed posterior urethral disruption injuries are highly amenable to successful reconstruction with excisional posterior urethroplasty via a perineal approach.

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Primary Realignment of Pelvic Fracture Urethral Injuries

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KEYWORDS

• Wounds • Urethra • Urethral stricture • Pelvic fracture

KEY POINTS

- Open primary repair of pelvic fracture urethral injuries (PFUIs) should not be performed due to unacceptably high blood loss and high rates of postoperative erectile dysfunction.
- Primary endoscopic realignment of PFUI is indicated for stable patients with PFUI, especially those with concomitant rectal and/or bladder injury.
- For unstable patients with PFUI, a suprapubic tube should be immediately placed. Endoscopic realignment can then be attempted during the first week after injury provided the patient has been appropriately stabilized.
- Even when primary realignment is successful, the majority of patients will develop a urethral stricture during the first year after the injury.

INTRODUCTION

Pelvic fracture urethral injury (PFUI) is an uncommon yet debilitating consequence of blunt pelvic trauma. The mechanism of these injuries involves major shearing forces at the bulbomembranous junction, resulting in avulsion of the urethra from the fixed urogenital diaphragm.¹ PFUI rates vary from 5% to 25% in small series^{2–4}; however, a recent review of the National Trauma Data Bank (NTDB) reported a lower prevalence of 1.54%.⁵ The initial management of these devastating injuries involves either primary urethral realignment or suprapubic cystostomy diversion followed by delayed urethroplasty. The potential advantages of primary urethral realignment include an earlier return to voiding, the possibility of avoiding future operative interventions, and better alignment of the proximal/distal urethral segments if an open urethroplasty is necessary in the future.^{6,7}

HISTORICAL PERSPECTIVE

PFUI management has changed significantly over the last 80 years. The earliest reported method of operative urethral repair was described by Young in 1929 and involved immediate, primary suturing of the disrupted urethral ends via a perineal approach.⁸ This method was abandoned in favor of the retroperitoneal approach because of concerns about placing the injured patient in a dorsal lithotomy position with a concomitant pelvic fracture.⁹ Immediate retroperitoneal exploration and primary urethral repair also passed out of favor because of unacceptably high blood loss and high rates of postoperative erectile dysfunction.⁴

Ormond and Cothran first described primary urethral realignment in 1934, by reapproximating the torn urethral ends with a catheter and encouraging re-epithelialization via catheter traction.¹⁰ This technique, referred to as railroading, involved

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advancing a catheter across the urethral defect in an antegrade or retrograde fashion to realign the urethra. The catheter remained in place for 4 to 8 weeks. Initially, the patient’s catheter was maintained on 500 grams of traction at a 45° angle for the first 5 to 7 days after injury in an effort to realign the proximal and distal urethral ends.¹ The theory supporting use of traction was to provide a scaffold for mucosal regeneration. Increased rates of incontinence were noted following the use of prolonged traction attributed to ischemic damage of the internal sphincter.¹¹ Canine studies performed in the 1960s also demonstrated that the transected canine posterior urethra did not undergo mucosal re-epithelialization. Instead fibrous tissue filled the intervening gap.¹²

Early techniques for urethral realignment were performed using either Davis interlocking sounds or magnetic sounds.¹³ These instruments are of historic interest used in the era before flexible cystoscopy. One sound was placed through the suprapubic tube tract, while the other was passed through the urethra. The sounds were advanced toward each other until the tips either linked together or were brought together via magnetic attraction. The tip of the SP tract sound then followed the penile sound until it exited the urethra, allowing a catheter to be advanced in a retrograde manner into the bladder. An SP tube could be placed for maximal drainage during healing. Primary urethral realignment was the standard of care for treatment of posterior urethral injuries from the 1930s until the 1960s. The technique later fell out of favor because of fear that primary urethral realignment caused further damage to the periprostatic tissue and neurovascular bundles, leading to impaired potency and continence.¹

In the mid-1950s, Endtner advocated for initial suprapubic cystostomy and no attempt at initial urethral manipulation.¹⁴ This would be followed by delayed, elective repair of the inevitable urethral stricture after 3 to 6 months of suprapubic catheter drainage.¹⁵ Although it generated a nearly 100% stricture rate,¹⁶ this delayed approach was the standard of care for the next 30 years.¹

Newer techniques pertaining to urethral realignment were introduced in the late 1980s. These techniques evolved into a combination of transurethral and transvesical endourologic procedures in conjunction with fluoroscopy.¹ This technique is postulated to reduce damage to erectile function compared with earlier methods of realignment, because there is no manipulation of the periprostatic tissues and neurovascular bundles.¹

INDICATIONS

Posterior urethral injury should be considered in male trauma patients who have sustained either a pelvic fracture or perineal trauma. Blood at the meatus should increase the level of suspicion. Basta and colleagues¹⁷ reported that 92% of male subjects with PFUI had inferomedial pubic bone fractures or pubic symphysis diastasis, and in 88% of subjects, the displacement was greater than 1 cm.

In patients who have sustained blunt trauma to the pelvis or perineum and who are clinically stable, a retrograde urethrogram (RUG) should be performed to characterize a potential urethral injury. If a urethral disruption injury is noted, then primary urethral alignment may be indicated. In patients in whom the index of suspicion for urethral injury is high, yet who are clinically unstable, the urologist may attempt placement of a urethral catheter followed by suprapubic catheter if urethral catheterization is unsuccessful. Retrograde urethrogram for diagnosis and injury staging can be performed after clinical stabilization of the patient.

Table 1 describes the American Association for the Surgery of Trauma (AAST) classification for urethral injuries along with their associated findings on retrograde urethrogram. In grades 1 and 2, the urethral mucosa is intact, and contrast does not extravasate during retrograde urethrogram. In these less severe injury patterns, gentle Foley catheter placement can be performed. Grades 3 to 5 injuries range in severity from partial to complete urethral lacerations (**Fig. 1**), and they are amenable to primary urethral realignment using the techniques outlined in the following

Table 1 AAST classification of urethral injuries		
Grade	Definition	Findings on RUG
1	Contusion	Normal RUG, blood at meatus
2	Stretch injury	Normal RUG, elongation of the urethra
3	Partial disruption	Extravasation of contrast, contrast into bladder
4	Complete disruption	Extravasation of contrast, <2 cm separation, no contrast in bladder
5	Complete disruption	Complete transection, >2 cm urethral separation or injury into prostate or vagina

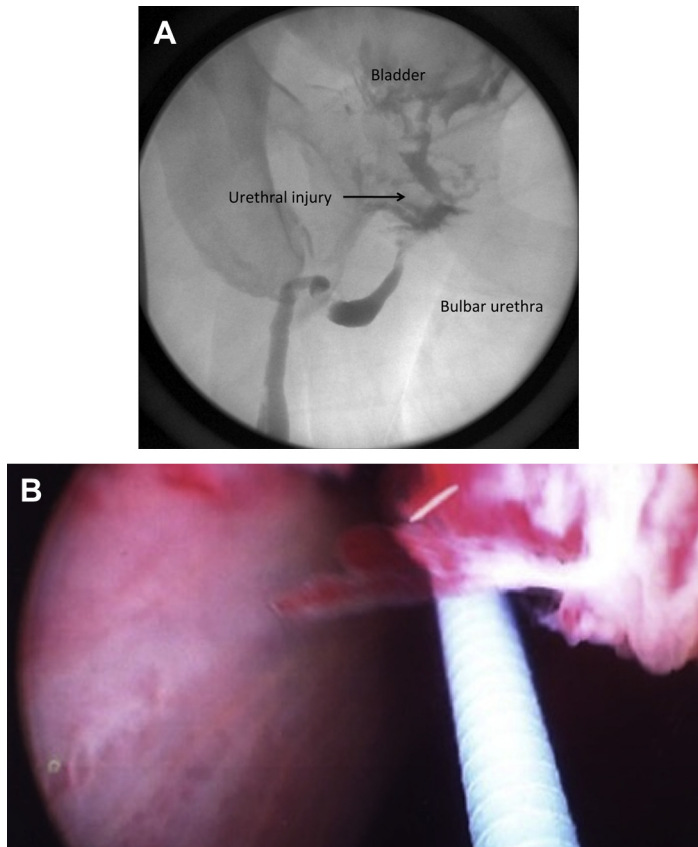


Fig. 1. (A) Retrograde urethrogram demonstrating partial urethral injury (AAST 3). (B) Endoscopic appearance of the lumen with preservation of a portion of the mucosa from 7 to 9 o'clock.

section. Specific indications for primary realignment in hemodynamically stable patients with PFUI include concomitant bladder and bladder neck injury (which makes SP cystostomy difficult or impossible), rectal injury (in which optimized drainage is recommended), and extreme displacement of the bladder and prostate from the membranous urethra (**Fig. 2**). **Fig. 3** outlines the authors' suggested algorithm for the management of PFUI.

TECHNIQUE: RETROGRADE AND ANTEGRADE/RETROGRADE

Primary urethral realignment for posterior urethral injuries can be performed using several techniques. The most commonly described techniques for primary urethral realignment include retrograde and antegrade/retrograde.

Retrograde Approach

A flexible cystoscope is advanced into the urethra to the injured area. In the setting of partial urethral injuries, the cystoscope may be able to navigate

the injury and be advanced directly into the bladder. Otherwise, a glide wire is passed through the damaged portion of the urethra into the bladder. Confirmation that the wire has traversed



Fig. 2. Cephalad displacement of the urinary bladder by pelvic hematoma in patient with complete urethral disruption (AAST 5).

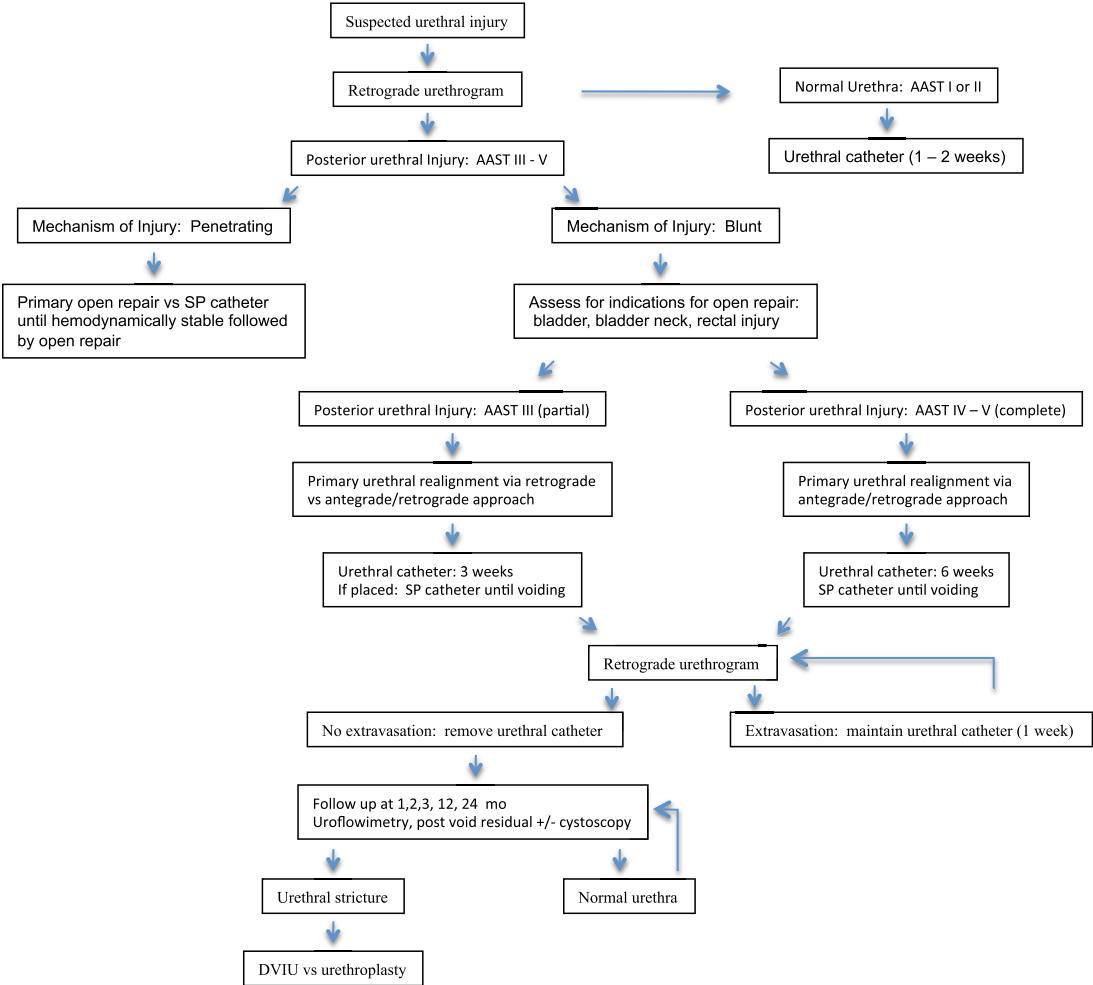


Fig. 3. Algorithm for the management of PFUI.

the injury and is coiled in the bladder is obtained by advancing a 5 F catheter over the wire. The guide wire is then removed leaving the 5 F catheter in place. Urine is then aspirated through the catheter, or, if fluoroscopy is available, a cystogram is performed. After confirmation of the 5 F catheter’s position, the guide wire is replaced, and a Council tip catheter is advanced over the wire into the bladder.

Antegrade/Retrograde Approach

This method employs an existing suprapubic tube tract, through which a flexible cystoscope is advanced to the bladder neck. A second cystoscope is advanced retrograde into the urethra. The 2 cystoscopes are advanced toward each other through the damaged portion of the urethra until the light from 1 cystoscope is visible by the other. Fluoroscopic images via a movable C-arm are helpful during this step in severe urethral

disruptions to assess the alignment of the 2 cystoscopes in the anterior/posterior and lateral planes. Once correctly aligned, a wire is advanced through 1 cystoscope into the working port of the other cystoscope, thus establishing access from the suprapubic tract through the injured urethra and out the urethral meatus. The cystoscopes are removed, and a Council tip urethral catheter is passed over the wire across the damaged urethra and into the bladder, where the balloon is inflated. A suprapubic catheter may be left for maximal urinary drainage during healing.

TECHNIQUE: ADDITIONAL CONSIDERATIONS
Timing of Primary Urethral Realignment

Following diagnosis of a partial urethral injury (AAST grade 3), the authors’ practice is to make 1 attempt at retrograde urethral catheter placement. If unsuccessful, they proceed with endoscopic

realignment via the retrograde approach outlined previously. Primary urethral realignment of a complete injury is often delayed 24 to 72 hours following injury, while the patient is stabilized in the trauma intensive care unit. The bladder is drained with a suprapubic catheter during this time. Delayed primary realignment can take place up to several days after the initial injury in a patient with a suprapubic catheter. The mean and median time to primary realignment in the authors' published series of primary urethral realignment patients was 2 days, with a range of 0 to 7 days.¹⁸

Placement of a Suprapubic Catheter

In the setting of delayed primary urethral realignment, the patient's bladder is decompressed with a suprapubic catheter. The suprapubic catheter is placed either by the urologist at bedside or under ultrasound guidance in interventional radiology. In pelvic trauma patients, the bladder may be displaced cephalad by significant pelvic hematoma, making ultrasound-guided suprapubic catheter placement a safer option (see Fig. 2).

Intraoperative Considerations: Setting, Positioning, Fluoroscopy, Antibiotics

The setting of the primary urethral realignment, at the bedside versus the operating room, is dictated by the stability of the patient and the need for other surgical procedures. To minimize trips to the operating room, the authors' preference is to perform primary urethral realignment in conjunction with other operative procedures, most commonly orthopedic. This provides several benefits, including close hemodynamic monitoring by anesthesia, a sterile environment, timely access to equipment and fluoroscopy, and the ability to perform an open repair of a possible concomitant bladder injury or bladder neck laceration.

The use of flexible cystoscopy allows for the patient to be positioned supine or in dorsal lithotomy position for both the retrograde or antegrade/retrograde approaches. When performed at bedside, the primary realignment is generally performed with the patient supine. Decisions regarding intraoperative positioning can be made with the input of the other surgical services involved in the planned procedures.

Intraoperative fluoroscopy is a helpful adjunct to both retrograde and antegrade/retrograde primary realignment. In the retrograde approach, fluoroscopy can confirm the proximal location of the wire in the bladder. In both approaches, a cystogram can be performed to evaluate for concomitant bladder or bladder neck injury. An intraperitoneal bladder injury or a bladder neck laceration are

both indications for open operative repair. During the antegrade/retrograde approach, fluoroscopy can confirm that the 2 cystoscopes are in the appropriate anterior/posterior and lateral plane.

Peri-procedural antibiotic prophylaxis is recommended with either a first-generation cephalosporin or a fluoroquinolone. Practice patterns differ depending on the duration of antibiotic prophylaxis.

Frequency of Technical Success

The reported urethral catheter placement rate via primary realignment is high, ranging from 70 to 93%.^{19–22} Other series indicate that if initial primary realignment is unsuccessful, delayed primary realignment in 2 to 3 days may be achievable, as tissue edema may have resolved, enhancing visibility.²⁰

Duration of Urethral Catheterization

The published duration of urethral catheterization varies from 3 to 6 weeks.^{3,4,19–26} The authors' practice is to maintain urethral catheterization for a minimum of 3 weeks for AAST grade 3 injuries and for 6 weeks for complete disruptions (AAST grade 4 and grade 5 injuries).¹⁸ Urethral catheters can be maintained longer if medically necessary as part of the patient's poly-trauma recovery. A pericatheter retrograde urethrogram or voiding cystourethrogram (VCUG) is performed at the time of catheter removal to confirm absence of urethral extravasation. Bladder drainage should be maintained via urethral catheter or suprapubic catheter until urethral extravasation has fully resolved to reduce the risk of scrotal abscess. If present, the suprapubic catheter can be capped after radiologic confirmation of urethral healing. After confirmation of successful voiding, the suprapubic catheter can be removed.

Surgeon preference dictates whether to leave a suprapubic catheter in addition to the urethral catheter. Orthopedists often prefer removal of a suprapubic catheter after urethral realignment if open reduction and internal fixation are performed for the associated pelvic fracture. If retrograde realignment is achieved, delayed replacement of the SP under controlled conditions may be considered in high-risk patients. If the suprapubic catheter is still present, the authors will cap the SP tube after confirmation of urethral healing and allow voiding per urethra. The SP tube can be removed once the patient is able to successfully void.

Follow-up Protocol

Among patients who failed primary urethral realignment, the mean time to failure was

79 days, with a range of 0 to 288 days.¹⁸ The authors' series indicates that although most patients fail within 6 months of urethral catheter removal, remote failures also occur. Given the high 79% stricture rate noted in their series, the authors' follow-up protocol includes uroflowmetry, postvoid residual and/or cystoscopic evaluation at 1, 2, 3, 12, and 24 months. Patients undergo immediate RUG and/or cystoscopy if symptoms of obstructive voiding manifest. The authors strongly recommend scheduled follow-up after all catheters are removed and do not have patients follow-up on an as-needed basis.

OUTCOMES

Webster and colleagues²⁷ performed a comprehensive literature review encompassing 538 cases of PFUI dating to the 1950s. The reported stricture rates for patients who underwent primary urethral realignment were 92% versus 100% for delayed open repair. However, it is difficult to interpret these results, as several series in this review used antiquated methods of urethral realignment. Two recent single-institution series comparing primary urethral realignment versus delayed open urethral repair reported stricture rates of 40 to 49% for urethral realignment versus 65% to 100% for open urethral repair (Table 2).^{6,7}

In the past decade, several single-institution studies of primary urethral realignment were published, reporting urethral stricture rates between 14% and 79% (mean 42%). These rates include patients who have required any additional maneuvers to achieve patency of the urethra, including

dilation, direct vision internal urethrotomy, and urethroplasty (see Table 2).^{6,7,18,20,25,26,28–31}

Of the patients in these single-institution series who developed a urethral stricture, 78% required endoscopic therapy such as dilation or DVIU, while 22% went on to require urethroplasty (Table 3).^{6,7,18,20,25,26,28–31} Of note, Olapade-Olaopa had patients perform prophylactic urethral dilations and had only 3 patients require urethroplasty.²⁹ In contrast, the authors' population preferred to undergo urethroplasty rather than multiple endoscopic procedures or repeat intermittent catheterization.¹⁸

COMPLICATIONS

Complications that are the direct result of primary urethral realignment are difficult to separate from the sequelae of the initial traumatic injury. Several series noted a small rate of complications such as: pelvic abscess (2%),³² urethroscrotal fistula (7%),³³ perineal abscess (16%–25%),^{30,34} and septicemia after delayed primary realignment (15%).²⁹ Failure to place a urethral catheter during primary realignment does not cause additional harm to the patient. In these patients, a suprapubic catheter is placed, and delayed urethroplasty is performed once urethral stricture develops.¹⁹ The technical success rates of urethral catheter placement are high; yet in 7% to 30% of patients, attempts at catheter placement are unsuccessful during primary urethral realignment.^{19–22,29}

A common concern in the historic and modern literature is whether endoscopic realignment makes subsequent urethroplasty more or less difficult. One small series of 7 patients found

Table 2 Outcomes of modern single-institution series of primary urethral realignment. Stricture rates denote all patients who required additional therapy to achieve urethral patency including dilation, direct vision internal urethrotomy, and urethroplasty					
Author/Year Published	Patients in Series	Average Follow-Up (months)	% Stricture	% Incont.	% ED
Leddy et al, ¹⁸ 2012	19	25	79	0	21
Sofer et al, ²⁶ 2010	11	52	45	0	55
Olapade-Olaopa et al, ²⁹ 2010	13	36	23	0	0
Hadjizacharia et al, ²⁰ 2008	21	7	14	NR	NR
Healy et al, ²⁸ 2007	8	41	40	0	40
Mouraviev et al, ⁶ 2005	57	106	49	18	34
Salehipour et al, ³⁰ 2005	25	20	24	0	16
Tazi et al, ³¹ 2003	36	34	42	0	19
Ku et al, ⁷ 2002	40	NR	53	16	25
Moudouni et al, ²⁵ 2001	27	83	52	0	15

Abbreviations: ED, erectile dysfunction; Incont., incontinence; NR, not reported.

Table 3
Interventions performed for the management of urethral stricture in the modern, single-institution series of primary urethral realignment

Authors/Year Published	Patients in Series	# with Stricture	# Needing U-Plasty	# Needing DVIU/Dilation	Ongoing CIC
Leddy et al, ¹⁸ 2012	19	14	11	3	0
Sofer et al, ²⁶ 2010	11	5	1	4	3
Olapade-Olaopa et al, ²⁹ 2010	13	3	0	2	10
Hadjizacharia et al, ²⁰ 2008	21	3	0	2	0
Healy et al, ²⁸ 2007	8	4	NR	NR	NR
Mouraviev et al, ⁶ 2005	57	28	14	28	0
Salehipour et al, ³⁰ 2005	25	6	0	6	0
Tazi et al, ³¹ 2003	36	15	2	13	0
Ku et al, ⁷ 2002	40	21	NR	NR	NR
Moudouni et al, ²⁵ 2001	27	12	2	12	0

Abbreviation: CIC, clean intermittent catheterization.

that urethroplasty after primary realignment was half as successful as the uninstrumented group (43% vs 85%).³⁵ This was thought to be the result of inflammation and fibrosis in the periurethral tissues as a result of instrumentation. Other authors have indicated that urethroplasty after primary urethral realignment was easier and more successful due to appropriate alignment of the proximal and distal urethral ends of the urethra.^{7,23} The authors' experience is that urethroplasty after primary realignment is feasible and has good technical success. In their series of 19 patients who underwent primary realignment, 11 underwent posterior urethroplasty. The authors did not note that posterior urethroplasty was more difficult following previous primary urethral realignment. Three patients in their series required operative maneuvers beyond urethral mobilization, including splitting corporal bodies in 2 patients and an inferior pubectomy on 1 patient. One patient required a urethral repair via the abdominoperineal approach; the other patients in the series underwent urethroplasty via a perineal approach. Mean follow-up for these patients is 3.0 years.¹⁸

Erectile function and urinary continence rates after primary urethral alignment have been reviewed in the urologic literature. In their comprehensive literature review published in 1983, Webster and colleagues²⁷ reported the rate of erectile dysfunction after urethral realignment was 52% versus 36% after suprapubic cystostomy and delayed open urethral repair. The reported rate of incontinence in this large review was 7% after realignment and 14% after suprapubic cystostomy and delayed open repair. This review demonstrates a high rate of erectile dysfunction in the realignment group versus the suprapubic

cystostomy group. However, a criticism of this review is that the technique for primary urethral realignment was not uniform, as the cohort was from multiple centers (15) and time periods (1961–1983). In addition there was no standardization of realignment technique or subsequent follow-up duration in many of the studies.

Two modern, single-institution series comparing rates of erectile dysfunction after primary urethral alignment versus suprapubic cystostomy followed by delayed open urethral repair found erectile dysfunction rates of 25% to 34% versus 15% to 42% and urinary incontinence rates of 0% to 18% versus 15% to 26%.^{6,7} The reported rate of postrealignment erectile dysfunction is much lower in the modern series, at 25% to 34% versus 52% in Webster's series. These rates were also similar to the rates of erectile dysfunction (15%–42%) found in the suprapubic cystostomy group. The rates of incontinence after primary urethral realignment remain relatively stable in all 3 series, at 0% to 18% versus 7% in Webster's large review.

Recent single institution series report postprimary realignment rates of erectile dysfunction of 0% to 55% and urinary incontinence rates of 0% to 18% (see [Table 2](#)).^{6,7,18,20,25,26,28–31} Data are not available regarding rates of erectile dysfunction before injury and before the primary realignment procedure; therefore, the authors cannot definitively comment on whether the erectile dysfunction is the result of the injury or the subsequent realignment.

LIMITATIONS

Although the published rates of urethral stricture after primary urethral realignment are high, the

procedure does save between 21% to 86% of men from subsequent urethral interventions.^{6,7,18,20,25,26,28-31} An additional 78% of patients who develop urethral stricture are saved an invasive surgical procedure such as a urethroplasty (see **Table 3**).

The failure rate aside, there are several limitations to primary urethral realignment. Primary urethral realignment can be a time-consuming procedure. The average published time for the retrograde approach is between 5 and 22 minutes.^{23,29,36} The authors noted the average time for the antegrade/retrograde approach to be longer at 74 minutes (range 10–284 minutes).¹⁸ Other series have reported the mean time for the antegrade/retrograde approach to be similar, at 40 to 75 minutes (range 30–145 minutes).^{25,26}

Primary urethral realignment can be a resource-intensive procedure for a several reasons. First, the antegrade/retrograde approach requires additional personnel, as 2 urologists are needed. In addition, close follow-up in the first 3 months after the injury is necessary because of high rates of stricture formation following urethral catheter removal. Lastly, there are issues related to the patient's poly-trauma, such as orthopedic injuries that may delay urological reconstruction if primary realignment fails. In such a circumstance, a suprapubic catheter may need to be reinserted in the operating room or by interventional radiology personnel. In such an instance, the patient will require frequent suprapubic catheter changes until an attempt at minimally invasive therapy or posterior urethroplasty can be made.

Urethral realignment is not indicated for primary treatment of patients with bladder neck or prostatic lacerations caused by pelvic fracture. These particular injuries are surgical emergencies and should be repaired during the index hospitalization once the patient is hemodynamically stable.³⁷ These patients continue to be managed with immediate open repair because of higher rates of sphincter incompetence or bladder neck contracture if the urothelial defect is not surgically repaired.

SUMMARY

In the past 80 years, debate has been ongoing in the urologic and trauma literature on the safest method of managing PFUI, the method that will result in the highest rates of continence and potency and the lowest rates of stricture formation. This debate has changed from immediate open surgical repair to rudimentary forms of urethral realignment to suprapubic drainage with delayed urethral stricture repair. In the past 30 years,

practice patterns have returned to favor early urethral realignment via endourologic methods. Based on what is available in the urologic literature, combined with the authors' own experience, primary endoscopic urethral realignment following PFUI results in high rates of symptomatic urethral stricture requiring further operative treatment. However, this technique spares a significant number of patients any further urethral intervention and an even greater number of patients the need for a subsequent urethroplasty. Thus, the authors continue to recommend primary urethral realignment after PFUI if it can be performed expediently and without subjecting the patient to additional risks. Close follow-up of these patients remains imperative after initial catheter removal because of cases of delayed stricture formation.

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Reconstruction of Traumatic and Reoperative Anterior Urethral Strictures via Excisional Techniques

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KEYWORDS

• Urethral stricture • Urethroplasty • Reoperative

KEY POINTS

- Reoperative urethroplasty may be compromised by poor tissue vascularity.
- Excision of poorly vascularized scar is important for successful reconstruction.

Urethroplasty is the gold standard for treatment of anterior urethral strictures. Reported success rates for excisional and primary anastomosis range from 86% to 99%.^{1–3} Success rates for substitution urethroplasty are lower, but remain high at 80% to 90%^{4–6} for oral mucosal grafts, and 75% to 87%^{7,8} for penile skin flaps. For patients with stricture recurrence, reoperative urethroplasty is rendered more challenging by the presence of dense scar tissue and poor tissue vascularity. Further, patients having prior substitution urethroplasty may have a concomitant shortage of donor sites for penile skin flap or oral mucosa graft. For these reasons, our approach to reoperative urethroplasty has centered on an excisional strategy when possible. The role of excisional reoperative urethroplasty is highlighted in this article.

PREOPERATIVE EVALUATION

Nearly all patients with stricture recurrence after urethral reconstruction present with recurrent

voiding symptoms. At first, imaging studies including retrograde urethrography (RUG) and voiding cystourethrography (VCUG), when possible, are performed because the radiographic appearance of strictures is known to change dramatically over time after intervention.⁹ Patients who have previously undergone urethroplasty, especially substitution techniques, often have irregularities on RUG. Urethroscopy is helpful to determine the caliber of the stricture in such cases; our practical general rule for questionable cases is that, if a 16-French flexible cystoscope can be passed through the area of narrowing, we do not offer surgical repair for those areas. In cases in which the patient has an obliterative stricture and a suprapubic tube has been placed, antegrade urethroscopy may be performed with the flexible cystoscope via the suprapubic tube tract.

Endoscopic management with urethrotomy or balloon dilation is performed if there are short, non-obliterative strictures. If a stricture is not amenable to endoscopic management or has failed previous

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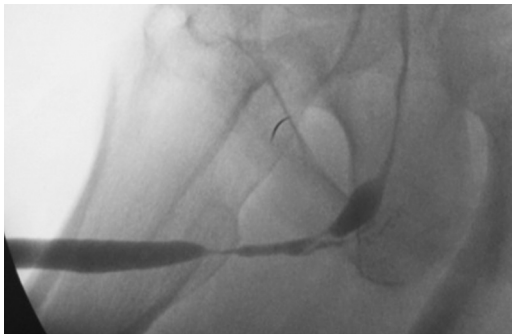
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A 53-year-old man with urethral stricture who underwent excision and primary anastomotic urethroplasty.

attempts at endoscopic treatment, reoperative urethral surgical reconstruction is performed.

SURGICAL TECHNIQUE

We attempt to perform reconstruction in a single stage. If more than one stricture is present, we adapt an ascending approach used for primary repair of synchronous strictures.¹⁰ Patient positioning is determined by the location of the stricture (supine for pendulous strictures, adjustable stirrups are used for dorsal lithotomy positioning for bulbar or synchronous strictures requiring concomitant perineal exposure). Serious position-related complications are more common with prolonged time in high lithotomy.¹¹ If a stricture is present in both the pendulous and bulbar urethra, we repair the pendulous portion first in low lithotomy before raising the legs to minimize time in high lithotomy.

THE CENTRAL ROLE OF EXCISIONAL TECHNIQUES

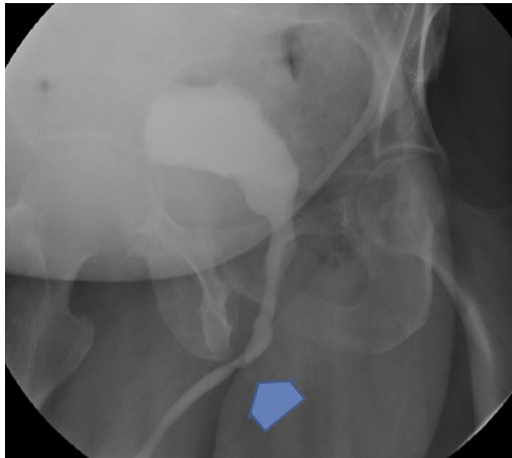
Scar tissue is poorly vascularized and does not heal normally. Thus, we think that resection of scar



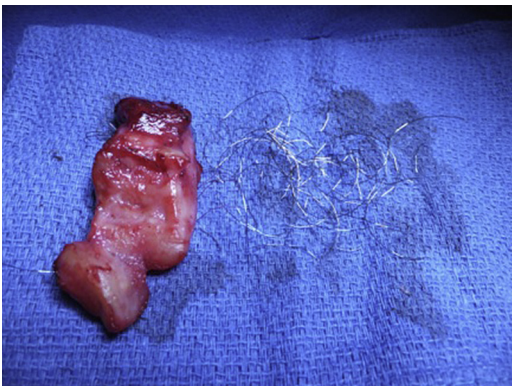
Recurrent stricture treated with urethral stent placed at an outside institution.

tissue is central for the success of urethral reconstruction. When possible, anastomoses should be performed across healthy tissue.

For bulbar strictures, excision and primary anastomosis (EPA) is performed whenever possible. We have found that strictures in the proximal bulbar urethra are especially amenable for this technique.¹² For the patient with posterior urethral stenosis who has previously failed an EPA with us, we usually perform a repeat perineal reconstruction emphasizing proximal exposure via corporal separation; sometimes a combined abdominal-perineal approach may be helpful, especially for children or complex cases. The anterior prostatic apex is mobilized off the pubis through the abdominal incision. The urethra is mobilized through the perineal incision. Mobilization through both incisions allows wide proximal exposure and complete scar excision with a tension-free anastomosis. We have found that most patients who have failed initial EPA can be salvaged with repeat EPA.



Recurrence of bulbar stricture (*arrow*).



The patient underwent scar excision, removal of UroLume, and repeat urethroplasty.



Postoperative voiding cystourethrogram after reoperative excision and primary anastomosis urethroplasty.

SUBSTITUTION URETHROPLASTY

When substitution urethroplasty has previously been performed in the bulbar urethra, the type of prior urethroplasty influences the repair. In patients who had a prior ventral onlay graft, we have found that the dorsal aspect of the urethra can be easily dissected from the triangular ligament and corpora cavernosa, thus facilitating straightforward EPA for short recurrences at either ends of the graft. If excessive stricture length precludes EPA, then we prefer to perform an augmented anastomotic urethroplasty with ventral onlay buccal mucosa graft or short penile skin minipatch.¹³ In patients who have had a dorsal onlay graft, the dorsal dissection is more difficult because the graft has been quilted to the corporal bodies. However, the abundant ventral bulbar spongiosum facilitates ventral onlay buccal as it normally would in nonreoperative scenarios.

We tend to prefer ventral onlay buccal mucosa graft for longer bulbar strictures because of the ease of exposure and suturing, and the stability of the corpus spongiosum. If there is a poor or absent urethral lumen to graft onto, and the stricture is too long to perform an EPA, overlapping buccal mucosa grafts has proved to be a reliable alternative to multistage reconstruction.¹⁴

For pendulous strictures, an 18-Fr bougie is placed in the urethra down to the location of the stricture. The urethra is incised ventrally at the midline until normal-caliber urethra is reached. The tissue quality of the urethral plate is examined and stricture length and width assessed. If the width of the urethral plate is at least 8 mm, and there is sufficient healthy non-hair-bearing skin, then we perform a circular fasciocutaneous penile flap.⁸ When the dorsal urethral plate is completely diseased, the portion of the dorsal plate containing

the worst scar is excised, the defect is shortened by roof-strip anastomosis if the dorsal defect can be approximated primarily, and a fasciocutaneous penile flap placed ventrally. If the dorsal defect is too long or severe, then a dorsal onlay buccal mucosa graft is placed in conjunction with a ventral fasciocutaneous penile flap.¹⁵ If patients do not have sufficient penile skin for a flap, we perform overlapping buccal mucosa grafts. A short dorsal buccal mucosa graft is placed within the severe defect, and a longer overlapping ventral graft is placed more broadly.¹⁴ When corpus spongiosum is unavailable for ventral graft coverage, tunica dartos, or tunica vaginalis are used, depending on location and tissue availability.

Multistage reconstruction is reserved for patients with long recurrent pendulous strictures who lack sufficient healthy penile skin for flaps, such as those with lichen sclerosus. For these rare cases, the scarred urethra is completely resected and a wide buccal mucosa graft is anastomosed to the proximal and distal end of the normal urethra and secured to the skin edges laterally. Quilting sutures are placed through the graft to fix it to the ventral side of the penis. A bolster dressing is secured with tie-over sutures and left in place for 5 days. The neourethra is then tubularized after approximately 6 months, provided that revision of either anastomosis or augmentation of areas of graft contract is not required.

POSTOPERATIVE FOLLOW-UP

Patients with reoperative stricture are at an increased risk of subsequent stricture recurrence, because the conditions that led to the initial failure (hypospadias, radiation therapy, lichen sclerosus) may still be present. We consequently perform voiding cystourethrogram at the time of catheter removal, and at 6 to 12 months. Patients with voiding symptoms are evaluated with flexible cystoscopy. We define urethroplasty failure as the inability to pass the 16-Fr flexible cystoscope past the obstruction, thus requiring endoscopic treatment or repeat urethroplasty.

SUCCESS OF REOPERATIVE URETHROPLASTY

In a recent University of California, San Francisco, series of 130 patients undergoing reoperative urethroplasty, the investigators reported a success rate of 67% for 1 procedure.¹⁶ Success after 2 procedures was 78% at a median follow-up of 55 months. The investigators performed a variety of repairs: anastomotic, fasciocutaneous penile flap, onlay graft, or combined technique. Anastomotic urethroplasty had lower failure rates

(15%) than other repairs, and was performed nearly half of the time. Longer strictures and complex repairs are more likely to fail. Hypospadias and lichen sclerosis are more likely to result in failure. Most failures occur within 2 years of surgery.

At our institution, we have observed that EPA for reoperative urethroplasty (in well-selected patients) is as successful as EPA performed primarily. Failure after prior substitution repairs can often be treated with EPA. With adequate proximal and distal mobilization, the stricture can be fully excised and an anastomotic repair performed.

SUMMARY

Reoperative urethroplasty is complicated by increased urethral and periurethral scar and the frequent persistence of comorbid conditions that caused the original failure. Nevertheless, by experienced clinicians, reoperative urethral reconstruction can be completed with success rates comparable with those of primary urethroplasty.

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Reconstruction of Radiation-induced Injuries of the Lower Urinary Tract

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KEYWORDS

• Radiation • Urethra • Stricture • Bladder neck contracture • Brachytherapy • Urethroplasty

KEY POINTS

- Radiation therapy for prostate cancer has been used with increased frequency in the past 2 decades. Higher radiation doses with modern techniques seem to be a significant risk factor for formation of urethral stricture, bladder neck contracture, and rectourethral fistula.
- Radiation delivered to the apex of the prostate during interstitial therapy is a significant risk factor for the formation of urethral stricture in the bulbar and membranous urethra. Dose modifications may limit formation of urethral stricture.
- Intensity-modulated radiation therapy has shown no increased risk of lower urinary tract injury compared with three-dimensional conformal external beam radiation therapy.
- Urethral stricture caused by radiation therapy is often located in the bulbar and membranous region. Most of these strictures are short, and most often can be repaired with excision and primary anastomosis. Longer strictures are amenable to substitution urethroplasty.
- Rectourethral fistula caused by radiation therapy is a serious complication. Urinary and bowel function can be successfully restored with reconstruction in many patients.

INTRODUCTION

Radiation therapy for the treatment of prostate cancer has been evolving since its introduction in the early twentieth century. The discovery of radioactivity, the weak form of uranium, by Henri Becquerel in 1896 and the discovery of radium by Marie and Pierre Curie in 1898 ushered in a new era in medical technologies.¹ Early knowledge of the effects of radiation on human tissue was identified through incidental exposures by early researchers. The subsequent medical applications with this new technology attempted to maximize the dose of radiation and minimize the effects on normal tissue. The following 2 decades led to refined technologies and techniques of

administration to prostate tissue through mainly intracavitary means that were used by prominent urologists of the era, including Hugh Hampton Young.² Benjamin Barringer is credited with pioneering the interstitial implantation techniques currently used via a perineal and suprapubic approach using glass-encapsulated radon.³ The 1930s saw the first use of external beam radiation therapy (EBRT). More effective use of external and interstitial therapies now relies on modern imaging techniques of computed tomography (CT) scans and transrectal ultrasound to maximize treatment and limit side effects.⁴

Prostate cancer is the most common non-skin-related malignancy of men in the United States. In 2012, an estimated 241,740 new cases

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will be diagnosed, which accounts for 29% of all new cancer diagnoses in men.⁵ According to the 2007 American Urological Association guidelines, use of either brachytherapy (BT) or EBRT may be used alone or in combination for first-line therapy for localized prostate cancer.⁶ Analysis of the CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) database, a national disease registry of more than 10,000 men, found that radiation therapy was used in more than 20% of newly diagnosed low-risk prostate cancer from 1993 to 2001.⁷ This same study also showed an increase in the use of BT from 4% to 22% during the study time period. The SEER (Surveillance, Epidemiology, and End Results) database, which includes primarily men more than the 65 years of age, has shown a rapid adoption of use in recent years of intensity-modulated radiation therapy (IMRT), a modality of EBRT that can deliver high doses of radiation. The use of IMRT compared with three-dimensional conformal EBRT increased from 0.15% of total men treated with EBRT in 2000 to 95.6% in 2008.⁸ Despite little knowledge of the long-term genitourinary morbidity, rapid adoption of high-dose IMRT and BT have become more prevalent in the treatment of prostate cancer.

Lower urinary tract injury caused by radiation treatment of pelvic malignancy includes formation of urethral stricture, bladder neck contracture (BNC), and rectourethral fistula (RUF). Each of these conditions can be a serious complication to the patient both physically and mentally. This article focuses on the pathophysiology, risk, evaluation, surgical reconstruction, and long-term considerations for patients with lower urinary tract injury caused by radiation therapy.

PATHOPHYSIOLOGY AND RISK FACTORS FOR LOWER URINARY TRACT INJURY

Radiation interacts with living cells in several ways that make it an effective cancer treatment. The effects may be divided into direct or indirect interactions with ionizing radiation. The direct interaction occurs when the energy from the photon directly damages either the cellular DNA and/or tissue protein. This damage leads to immediate cell death or mutation of the DNA. The indirect interaction occurs when the ionizing radiation interacts with water in the cell and leads to the formation of free radicals that interact with enzymes leading to cell death or future mutation. Both of these interactions lead to cellular injury that can cause division delay, reproductive failure, or interphase death through the apoptosis mechanism, which is more common in rapidly dividing cells.⁹ These interactions and resultant cellular injury are dose

dependent and occur in a linear threshold model. When normal tissue is damaged with exposure greater than the injury threshold, several changes occur that result in a cycle of scar and subsequent healing. Damage to basement membranes of vessels can lead to occlusion, thrombosis, and eventually reduced neovascularization.¹⁰ The subsequent fibrosis is caused by an increase of fibroblasts that no longer make mature collagen, which accounts for the atrophy and contraction of the tissue.¹¹

Urethral stricture results from replacement of the corpus spongiosum with fibrosis and resultant occlusion of the urethral lumen.¹² With a more thorough understanding of radiation biology it is logical that increases in radiation doses would result in a higher rate of urethral stricture. High-dose-rate BT (HDRBT) and EBRT, either alone or in combination, have been used to achieve higher disease-free survival for the treatment of prostate cancer.^{4,13–16} This strategy has developed out of improved technology and imaging techniques that allow more focused concentration of radiation to the intended tissue. Data from the CaPSURE database showed the stricture rate for BT to be 1.8%, EBRT 1.7%, and combined therapy 5.2%.¹⁷ Another more recent study compared the rate of stricture formation in 1903 patients after EBRT, low-dose-rate BT, and HDRBT. The rates of urethral stricture formation were 2%, 4%, and 11% respectively, indicating that despite modern imaging techniques and modifications the amount of radiation damage delivered to normal tissue is significant.¹⁸

The use of HDRBT has shown a high incidence of urethral stricture formation. Sullivan and colleagues¹⁹ showed that after HDRBT the actuarial rate of urethral stricture formation at 6 years was estimated to be 12% for all urethral locations and 10.8% for the bulbomembranous location. Overall, the investigators concluded that 90% of urethral strictures following HDRBT occur in the bulbomembranous region. When combined with EBRT, HDRBT has a similar rate of stricture formation as HDRBT alone at 11.8%.¹⁴

As expected, the dose of radiation delivered to the urethra has been shown to be a significant risk factor in the development of urethral stricture as well as the location of the delivered radiation dosage. Merrick and colleagues²⁰ has shown that, in patients with urethral stricture formation following BT, the dose delivered to the apex of the prostate was significantly higher than in case-controlled patients who did not form urethral strictures. By limiting the dosage to the apex of the prostate, the investigators showed a relative risk reduction of stricture formation of greater than 30%. Earley and colleagues²¹ found that the radiation delivered by

low-dose-rate BT within 5 mm of the urethra at the apex of the prostate was significant. Of the patients treated in this study, the 6.5% who formed urethral stricture had roughly 30% more dosage delivered to the apex of the prostate.

The amount of radiation delivered per treatment also affects the rate of urethral stricture following treatment. When 18 to 20 Gy of radiation were delivered by HDRBT over 2, 3, or 4 fractionated dosages, the stricture rate was different. The fractionated dosages were delivered during a single hospital admission with at least 6 hours between treatments. The urethral stricture rate increased to 31.6% when delivered over 2 treatments, compared with 3.4% for 3 treatments and 2.3% for 4 treatments. The investigators concluded that the amount delivered per treatment was the most significant factor in urethral stricture formation, which led to a change in their treatment algorithm.²²

EBRT may be delivered in a variety of ways. The most common modern techniques are three-dimensional conformal therapy and IMRT, which have a similarly low rate of stricture formation, typically reported to be less than 3%.^{17,18,23} However men who have undergone previous transurethral resection of the prostate before conformal EBRT have an increased risk of urethral stricture formation ranging from 4% to 16%.^{24,25} Another high-risk group for urethral stricture formation includes men who undergo adjuvant EBRT therapy for high-risk prostate cancer following radical prostatectomy in whom the rate of urethral stricture formation is reported to be as high as 17%.²⁶

Proton beam therapy (PBT) uses high-velocity particles instead of photons to deliver energy to the prostate. In theory, PBT delivers less energy to normal tissue because the proton's energy is dissipated at preset depths depending on the velocity of the proton.²⁷ Genitourinary complications seem to be comparable with external beam therapies, although limited data make these rates difficult to compare. In one phase III clinical trial that compared high-dose EBRT alone or with an additional boost of conformal PBT, the rate of urethral stricture increased from 8% of 99 patients who received EBRT therapy alone to 19% of 103 patients who received a PBT boost to EBRT.²⁸

Data on the rate of formation of BNC after radiation are limited; however, it is estimated to be between 2% and 12%.^{17,29-31} The risk factors for the development of BNC following radiation have not been studied as extensively as urethral stricture formation, but it can be inferred that similar factors such as the dose and location of radiation delivery play a major role.

RUF formation following radiation therapy has been reported with greater frequency in the

literature over the last decade. The process that results in RUF formation following radiation is speculated to be the result of fibrosis and microvascular injury leading to mucosal ulcers and eventual fistulization. Lane and colleagues³² concluded that, before 1997, radiation therapy accounted for only 12% of the total RUF. After 1997, RUF caused by radiation increased to 49.6% of the total RUF reported in the literature. The investigators concluded that reporting bias may have been partially responsible for this finding but likely the increase in use of radiation therapy for prostate cancer was also responsible. Nonetheless, the overall incidence of RUF is uncommon after EBRT (0%–0.6%)^{33,34} and after BT (0.3%–3%).^{30,35-37} As with radiation-induced urethral stricture, this process seems to be dose dependent, but this has not been confirmed.

The risk of RUF may increase after endoscopic or open manipulation of the urethra, prostate, or rectum following radiation therapy. In one study, RUF was linked to postradiation transurethral resection of the prostate in 38%, postradiation rectal biopsy in 38%, and argon beam therapy for postradiation proctitis in 13% of patients.³⁸ This same study also showed a high rate of concomitant urethral and rectal strictures, which may cause high-pressure elimination, a contributing factor in the development of RUF.

Salvage therapy after primary radiotherapy for recurrent prostate cancer significantly increases genitourinary complications. Salvage radical prostatectomy can result in an anastomotic urethral stricture rate of up to 41%^{39,40} with an average rate of 20%.⁴¹ Salvage cryotherapy results in urethral sloughing and subsequent stricture formation in 15% of patients,^{42,43} BNC in up to 28% of patients,^{43,44} and RUF in 3.4% of patients.^{45,46} Salvage BT after primary radiotherapy results in grade 3 to 4 genitourinary toxicity in 14% to 47% of patients,^{47,48} but specific percentages of urethral stricture are difficult to determine. Following salvage BT, RUF has been reported to occur in up to 12% of patients.^{41,49} High-intensity focused ultrasound (HIFU), when used for biochemical recurrence following radiation therapy, results in BNC formation in 17% of patients and RUF formation in up to 16% of cases.⁴¹

PATIENT EVALUATION

Multiple urinary symptoms may occur as a result of radiation injury to the lower urinary tract. Storage-related symptoms such as frequency, urgency, and urge-related incontinence occur mainly as a result of bladder damage and loss of capacity; postmicturition and obstructive symptoms such

as hesitancy, postvoid dribbling, and weakened stream occur mostly secondary to occlusion of the lower urinary tract. Up to 70% of patients may report these symptoms in a progressive manner that may even manifest months or years after the initial radiation injury.¹² A validated questionnaire specific to urethral strictures has not been fully established; however, Jackson and colleagues⁵⁰ provided methodology and initial results for a urethral stricture-specific questionnaire with good content and criterion validity to assess urinary complaints. When fully developed, such a tool may aid in the noninvasive evaluation and follow-up for patients with urethral stricture disease. Urinary tract infection, hematuria, or acute urinary retention may also occur in these patients, but less commonly as the presenting complaint. Physical examination can be used to determine urethral meatus patency and may reveal suprapubic fullness if urinary obstruction is present. On rectal examination, a RUF may be palpated, especially if the defect is large.

Diagnostic studies useful for the evaluation of urethral strictures and BNC consist of urinary flow studies, urodynamics, endoscopic studies, and radiologic evaluation. Urinary flow studies are commonly performed and often show a flat curve with low urinary flow rate in men with obstruction from BNC or urethral stricture disease.⁵¹ Urodynamic studies may be helpful to determine whether a patient is a candidate for reconstructive repair of BNC following radiation therapy, although catheter placement may be challenging. For patients with bladder volumes less than 200 mL or severe detrusor instability, conservative measures to increase bladder volume may be attempted before reconstruction. However, other options such as bladder augmentation before reconstruction or urinary diversion can be discussed with the patient.^{52,53} Postvoid residual may also be performed but this study is nonspecific and may be subject to user variation.⁵⁴ Retrograde urethrography offers the ability to determine the length and location of the obstruction (**Figs. 1** and **2**). If necessary, voiding cystourethrogram allows for full evaluation of the posterior urethra as well as the urethra proximal to the stricture if retrograde urethrogram is inconclusive.¹² If a suprapubic tube is present, simultaneous antegrade endoscopy and retrograde urethrography can be performed (**Fig. 3**). MRI and CT scan rarely provide useful staging information before urethroplasty. Ultrasound of the urethral stricture may also provide useful staging information about the extent of the spongiofibrosis.⁵⁵

RUF is often more obvious than urethral stricture or BNC and presents with urine persistently leaking from the rectum. The fistula typically develops

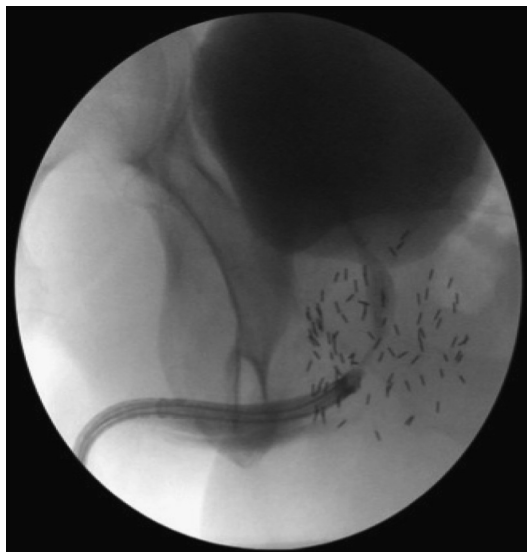


Fig. 1. A stricture involving the bulbar and membranous urethra following BT.

several months to years after treatment with radiation. In addition to the urinary leakage, patients may present with pneumaturia, dysuria, perineal pain, or pelvic pain. Fecaluria is less common with RUF than colovesical fistula because of the higher pressure of the urethra compared with the bowel.⁵⁶ Digital rectal examination may assist with the diagnosis if the defect is large. Retrograde urethrogram and cystogram should be performed to confirm the suspected diagnosis and to determine whether there is a concomitant urethral



Fig. 2. Retrograde urethrogram (RUG) showing a radiation-induced BNC following radical prostatectomy and adjuvant EBRT.

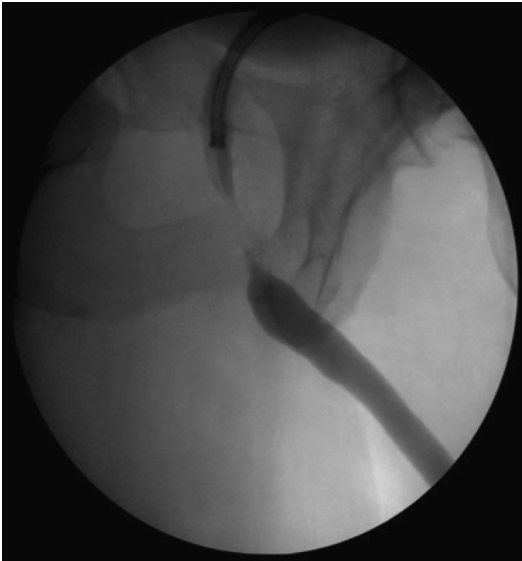


Fig. 3. Combined antegrade endoscopy and RUG to delineate the extent of a radiation-induced urethral stricture.

stricture or BNC in addition to the RUF (**Fig. 4**). Proctoscopy and cystoscopy should also be performed under anesthesia to fully delineate the location and extent of the fistula and guide planning. Examination should also focus on evaluation of a rectal stricture, because almost all patients who are treated with BT have some degree of rectal stenosis.⁵⁷ Biopsy should be taken of all fistula tracts before surgery to assess for cancer recurrence at the fistula site. Abdominal and pelvic imaging with CT or magnetic resonance imaging



Fig. 4. RUG showing a rectourethral fistula and concomitant urethral stricture.

also helps to delineate the location of the fistula and the degree of surrounding tissue viability.³²

Diversion with a colostomy or ileostomy has been reported before or at the time of definitive reconstructive management for tissue healing and symptomatic improvement.^{32,38,58,59} Although it has been stated that all patients who develop a complex RUF following radiation therapy should undergo fecal diversion, this has not been established.⁶⁰ Mundy and Andrich⁵⁶ reported a series of radiation-induced RUF repaired with and without fecal diversion. The investigators showed no impact of preoperative fecal diversion on the success of the repair. It was postulated by the investigators that, if fecal diversion was not performed after the initial diagnosis, then a colostomy was not necessary at the time of repair. In general, the decision to perform fecal diversion should be based on the viability of the tissue surrounding the RUF.⁶¹ Counseling is important with these patients because urinary and fecal diversion can be used as definitive long-term management in lieu of reconstruction for symptomatic relief.^{38,58} Permanent fecal diversion may be considered in patients with extensive damage to the rectum and anal sphincter with a low probability of fecal continence after surgery.

When considering reconstruction of the urinary tract for RUF, urodynamic studies should be considered. Urodynamics may be difficult to obtain in patients with RUF, because the bladder may not hold adequate volumes because of urinary leakage. Nonetheless an assessment of bladder capacity is necessary. As with patients diagnosed with radiation-induced urethral stricture or BNC, men with a radiation-induced RUF and a significantly limited bladder capacity are often best suited for urinary diversion with cystectomy and ileal conduit.

Sexual function should be evaluated and assessed before and following reconstruction of lower urinary tract injuries caused by radiation. Sexual function, as assessed by patient report, was preserved in the 50% of patients undergoing anterior urethroplasty for radiation-induced urethral stricture who reported normal sexual function before surgery. However, validated patient-reported outcome measures were not used in this study.⁶² The International Index of Erectile Function (IIEF) questionnaire has been helpful in the assessment of men with urethral stricture of various causes. Erickson and colleagues⁶³ reported on a prospective analysis of 52 men who underwent urethroplasty for anterior urethral stricture disease. Thirty-eight percent (20/52) of patients experienced worsened erectile function after surgery. At 6 months following urethroplasty, 90% (18/20) of these men recovered their preoperative level of sexual function. Ejaculatory

function also seems to be preserved following urethroplasty for anterior urethral stricture disease of various causes. Prospective use of the Male Sexual Health Questionnaire has shown that 89% (38/43) of men report stable or improved ejaculatory function after surgery.⁶⁴ Ejaculatory function has not been evaluated in men with radiation-induced urethral stricture diseases. Doppler ultrasound may prove useful to assess penile blood flow before urethroplasty for stricture disease, but its usefulness to assess erectile function in patients with radiation injury to the lower urinary tract remains unknown. The impact of lower urinary tract reconstruction on sexual function in men with radiation-induced BNC or RUF remains to be studied.

URETHRAL STRICTURE SURGICAL RECONSTRUCTION

Dilation and endoscopic incision of urethral stricture caused by radiation is often reported with high success in the radiation oncology literature, although there is a paucity of data on long-term follow-up and recurrence following these endoscopic options.^{19,20,65} A limited number of studies have specifically addressed outcomes following urethroplasty in men with urethral stricture formation after radiation therapy.

The first report on reconstructive outcomes in men with radiation-induced urethral stricture disease focused on a small single-center series that showed that excision and primary anastomosis (EPA) was effective for strictures less than 2 cm in 6 of 7 patients. One patient who underwent a genital skin fasciocutaneous flap for a stricture less than 2 cm recurred. Time to recurrence, incontinence, and sexual function outcomes were not reported in this study.⁶⁶

A retrospective, multiinstitutional study reported on the follow-up of 30 patients who underwent reconstructive repair of urethral strictures following radiation therapy for prostate cancer. The study population consisted of 15 men (50%) treated with EBRT alone, 7 men (24%) treated with BT alone, and 8 patients (26%) treated with combined EBRT and BT. All of the urethral strictures were in the bulbomembranous urethra, averaging 2.9 cm in length with a range of 1.5 cm to 7 cm. EPA was used in 24/30 (80%) patients with an average stricture length of 3 cm. The remaining repairs consisted of genital fasciocutaneous skin flap use in 4/30 (13%) and buccal graft onlay in 2/10 (7%) patients, with an average stricture length of 4.3 cm. A total of 27% (9/30) of the patients in this series recurred at a mean of 5.1 months and 2 required balloon dilation. No patients required eventual urinary diversion. The new onset of

incontinence was seen in 50% (15/30) of men, and resolved in 3/30 (10%). An artificial urinary sphincter (AUS) was placed in 4/30 (13%) men. Erectile function was preserved in the men who reported normal preoperative function.⁶²

In the largest reported single series to date, Glass and colleagues⁶⁷ retrospectively reported on a total of 29 men with urethral stricture formation following radiation treatment of prostate cancer. Eleven patients treated with EBRT alone (38%) were included; radical prostatectomy followed by adjuvant EBRT, 7 (24%); combined EBRT/BT in 7 (24%); and BT alone 4 (14%). The average stricture length was 2.6 cm in the series, with location identified in the bulbar urethra, 12/29 (41%); membranous urethra, 12/29 (41%); bladder neck, 3/29 (10%); and panurethral, 2/29 (7%). EPA was performed in 22/29 (76%) patients, whereas 5/29 (17%) underwent substitution urethroplasty with buccal graft, and 2/29 (7%) with fasciocutaneous flap onlay. One EPA, 1 buccal graft, and 1 fasciocutaneous flap onlay case each recurred for an overall series success rate of approximately 90%. The new onset of urinary incontinence was reported in only 2 patients (7%) with 1 patient opting for an AUS to manage urinary incontinence. Erectile function was not reported before or after surgery.

Although limited in patient number and design, these studies show acceptable success rate with EPA in patients undergoing urethroplasty for short, proximally located, radiation-induced urethral strictures. Substitution urethroplasty seems to be most effective for anatomically more distal strictures in the bulbar or penile urethral and those of greater length. Longer follow-up is needed to assess the durability of these outcomes.

The technical approach for radiation-induced urethral stricture disease is similar to that for other causes. For proximally located stricture disease, the patient may be placed in the exaggerated or dorsal lithotomy position for perineal exposure of the urethra to the level of the prostate. Mobilization of the urethra off the corpora cavernosa to the proximal penile urethra is often necessary to achieve a tension-free anastomosis. Other extensive maneuvers such as splitting the corpora cavernosa or removal of the pubic bone have been described but are rarely necessary.⁶⁸

Complete scar excision to the level of the prostatic apex is often necessary in patients with bulbomembranous stricture disease. At times, the ability to place sutures in the apex of the prostate for a primary anastomosis with the bulbar urethra may be limited with standard needle drivers. Use of the Capiro device (Boston Scientific) can assist in placing these proximal sutures at the desired depth (Fig. 5). The device was originally designed



Fig. 5. The Capiro device with a preloaded suture.

for placement of sutures in complex female urology procedures. The curve of the Capiro device makes it ideal for passing suture at an oblique angle, and is superior to other suture-passing devices used in laparoscopy that only pass suture at a right angle. With these maneuvers it is possible to properly place sutures into the mucosa of the apical prostate to create a watertight anastomosis with the bulbar urethra.

BLADDER NECK RECONSTRUCTION

BNC after radiation therapy has unique considerations of management compared with BNC following radical prostatectomy. The patients undergoing radiation therapy who develop BNC often cannot tolerate a suprapubic tube and are at high risk of bladder instability as well as low bladder capacity.⁵³ There are limited data on outcomes following open reconstruction for recalcitrant BNC in men with a history of radiation for treatment of prostate cancer. The reconstructive approaches and outcomes following BNC of various causes, including radiation therapy, are summarized in **Table 1**. For bladder neck reconstruction following primary radiation therapy for prostate cancer, salvage prostatectomy (SP) can be considered for reconstructive therapy following failure of endoscopic management. Mundy and Andrich⁵³ reported on 9 patients undergoing SP for BNC that resulted in 3 patients developing recurrent BNC and 1 patient requiring an AUS for management of incontinence. For patients undergoing open SP for biochemical recurrence after radiation therapy, the de novo BNC formation rate was 41% following surgery in one large single-center study.⁴⁰ Robotic SP is also feasible and may have less morbidity than open SP with a BNC incidence of 9%.⁶⁹

Almost all patients in both the open and robotic SP series developed some degree of urinary incontinence, with only 30% regaining continence at 3 years in the open SP series.^{40,69} In men with pre-operative sexual potency, approximately 30% remained potent in both the open SP and the robotic SP series.^{40,69}

In the setting of a recalcitrant BNC following radical prostatectomy with adjuvant EBRT, the reconstruction of a patent vesicourethral anastomosis may involve a combined abdominoperineal, abdominal, or a perineal approach. Reconstructive surgery is best considered only after multiple failed attempts at endoscopic management including cold or hot knife incision, laser ablation, dilation, limited transurethral resection, or failed urethral stent placement. Early reports of open reconstruction involved a combined abdominoperineal approach that used pubectomy, and the use of omentum or rectus muscle to support a primary anastomosis or a penile fasciocutaneous flap for onlay over the stricturotomy.^{70,71} Subsequent larger series described reconstruction using a combined open abdominal or perineal approach along with endoscopic techniques to reduce overall operative time and morbidity.^{72,73} Outcomes in these series were variable and no standardization of approach for these patients has been established.

In those men with a lengthy BNC following radical prostatectomy and radiation, an abdominoperineal approach is an effective reconstructive option. Often a transpubic approach is performed to access the stenosed section of the bladder neck and membranous urethra. A perineal approach is used to obtain access to the bulbar urethra for mobilization and eventual anastomosis. The primary advantage of this combined approach includes the ability to excise all diseased tissue to create a tension-free primary anastomosis in an irradiated field compared with a perineal or transpubic approach alone (**Fig. 6**).

A transpubic approach can be used for limited BNC to preserve the urethral sphincter and continence. Complete or partial pubectomy is performed to obtain access to the bladder neck with limited mobilization of the urethra and bladder to avoid extensive tissue damage or rectal injury in the radiated field. In the author's experience, the use of an anterior bladder wall advancement flap has proved successful to augment BNC of up to 3 cm (**Fig. 7**). Pfalzgraf and colleagues⁷² reported a series of 20 men treated for BNC after prostatectomy with an intact external urethral sphincter. A retropubic approach and use of a Grunewald retractor to assist in the placement of anastomotic sutures for a primary anastomosis was used in all patients. An initial patency rate of 60% was

Table 1 Outcomes of reconstruction for recalcitrant BNC						
Study	# Patients	Approach	Cause (N)	Tissue Interposition (N)	Patency (%)	Postoperative Urinary Incontinence (%)
Schlossberg et al, ⁷⁰ 1995	2	Abdominoperineal	RRP (2)	Omental flap (2)	100	0
Wessells et al, ⁷¹ 1998	4	Abdominoperineal (1) Transpubic (2) Perineal (1)	RRP (1) SP (1) RPP (2)	Omental flap (1) Penile skin flap (1) Rectus flap (1)	100	100
Mundy et al, ⁵³ 2012	9	Retropubic SP (9)	EBRT±BT (9)	0	66	11
Pfalzgraf et al, ⁷² 2011	20	Retropubic (VUA)	RRP (20)	0	60	33
Simonato et al, ⁷³ 2012	11	Perineal (VUA)	LRP (3) RRP (8)	0	100	94

Abbreviations: LRP, laparoscopic radical prostatectomy; RRP, radical retropubic prostatectomy; SP, salvage prostatectomy; VUA, vesicourethral anastomosis.

achieved, with additional endoscopic resection increasing the patency rate to 95%. Urinary incontinence was reported at 33% following successful repair.

RECTOURETHRAL FISTULA REPAIR

Postsurgical RUF in the absence of radiation therapy is rare, with an incidence of less than 1% after radical prostatectomy.⁷⁴ If surgical repair is warranted after a trial of conservative therapy, less

invasive approaches may be used, such as a transanal or transanosphincteric approach, with success rates approaching 100%. These operations are performed in the prone position with primary closure of the prostatic and rectal defect as well as mucosal advancement flaps.^{60,75,76} In contrast, radiation-induced RUF mostly does not respond to conservative methods and more often requires reconstruction and tissue interposition for successful resolution.⁷⁷ Urethral stricture and BNC are present concomitantly in 28% of patients

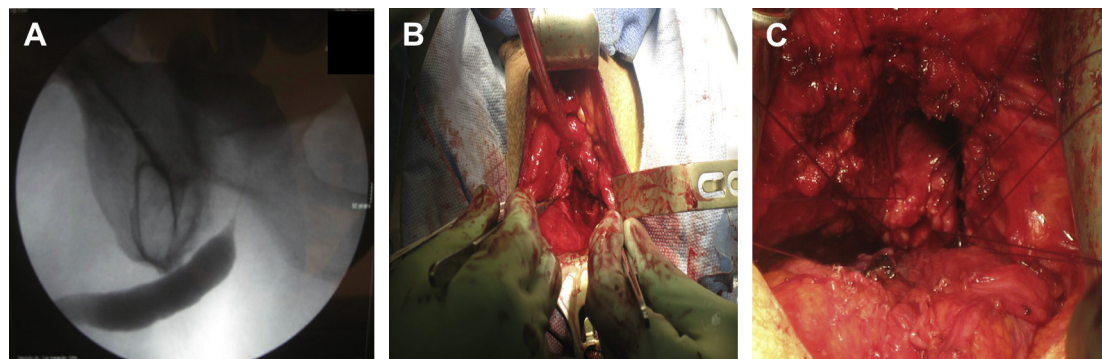


Fig. 6. (A) RUG of lengthy BNC after radical prostatectomy and adjuvant EBRT. (B) Perineal approach to mobilize the urethra. (C) Transpubic approach to resect contracture and complete the anastomosis of the bulbar urethra and bladder neck.

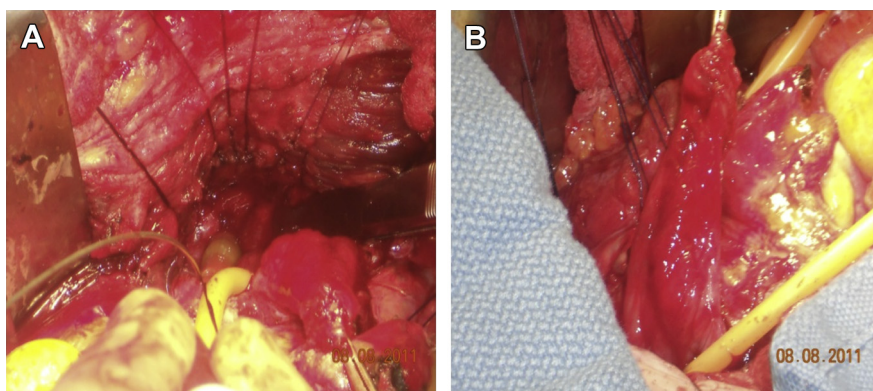


Fig. 7. (A) Urethrotomy of a BNC. (B) Anterior bladder wall advancement flap for closure of the urethrotomy.

with RUF following radiation therapy, which further complicates surgical repair in this cohort.⁵⁹

Approaches for the repair of radiation-induced RUF consist of transanal, transanosphincteric, transperineal, and abdominal techniques. In the setting of a radiation-induced RUF, reconstructive considerations include initial fecal and urinary diversion, adequate exposure of the fistula, the use of well-vascularized tissue for interposition, and repair of concomitant disorders of the urethra and rectum. The likelihood of success is subject to the experience of the surgeon(s) involved. Large studies specifically addressing approaches and outcomes after reconstruction for radiation-induced RUF formation are limited in number, with some outcome variables not fully available (**Table 2**).

Less invasive techniques more commonly used for uncomplicated RUF have limitations that make repairs with this approach technically difficult or inadequate for radiation-induced RUF. A transanal approach is discouraged for radiation-induced RUF repair because of limited exposure and inability to access the lower urinary tract other than the prostate for repair. A transanosphincteric (York-Mason) approach allows for better exposure of the RUF with limited permanent damage to the anal sphincter. This approach also provides adequate space for the use of tissue interposition with gracilis muscle flaps, rectal advancement flaps, and multilayered closure. However, similar to the transanal approach, larger or complex defects are challenging with the transanosphincteric approach, because strictures of the bulbar and membranous urethra often cannot be fully exposed and repaired.⁵⁹

The transperineal approach is most commonly used for management of large, complex RUF associated with radiation treatment.^{56,59,66,78} Advantages of this approach include wide exposure for large fistulae and the ability to address concomitant disorders of the rectum and urethra. Tissue

interposition for large defects of the urethra can be performed adequately with graft of flap, and the ability to interpose gracilis flaps is readily available. Small rectal defects can be repaired directly with primary closure. An abdominoperineal resection with staged coloanal anastomosis can be used if the tissue of the rectum is not adequate for primary closure or a rectal stricture is present.³²

An abdominal approach is not commonly used, but it can be used in the setting of a RUF after radiation therapy that necessitates SP in the same setting as repair. This approach does not allow access to the anterior urethra or distal rectum, which necessitates perineal exposure for concomitant anterior urethral stricture or RUF not located in the prostatic urethra. The use of omentum and peritoneum can be used with this approach to interpose this tissue between the rectal repair and vesicourethral anastomosis.⁵⁶

Long-term quality of life (QOL) and functional outcome of the fecal and urinary systems after complex RUF repair have only recently been addressed in the literature. Samplaski and colleagues⁷⁹ presented the results of 12 patients who completed symptom-specific QOL questionnaires concerning urinary and fecal outcome following successful transperineal repair of a complex RUF repair with gracilis muscle interposition. RUF cause was radical prostatectomy in 4 (33%), BT alone in 3 (25%), combined EBRT and BT in 3 (25%), cryoablation in 1 (~8%), cryoablation and EBRT in 1 (~8%), and imperforate anus in 1 (~8%). The fecal function impact on patient QOL was generally better than urinary function. Only 4 of 12 (25%) patients who had fecal incontinence were managed with adult diapers and did not report significant social embarrassment. In contrast, 9 of 12 (75%) patients reported some degree of urinary incontinence, with 4 (33%) having significant stress-related incontinence and 4 (33%) having significant urge-related incontinence. Only 2

Table 2
Outcomes after reconstruction for RUF following radiation therapy

Study	# Patients	Approach (N)	Cause (N)	Tissue Interposition (N)	Recurrence (%)
Hadley et al, ⁶⁰ 2012	7	Transanosphincteric	BT+EBRT (7)	Gracilis flap (1)	57
Mundy et al, ⁵⁶ 2011	17	Abdominal SP (8) Perineal (3) Abdominoperineal (6)	BT (3) EBRT (4) BT+EBRT (10)	Omentum (15) Gracilis (2)	0
Lane et al, ³² 2006	13	Transanal (2) Perineal (11)	BT (5) EBRT (2) BT+EBRT (6)	Omentum (2) Gracilis flap (7)	100 Transanal, 0 Perineal
Vanni et al, ⁵⁹ 2010	39	Perineal	BT (13) EBRT (7) BT+EBRT (12) BT+EBRT+CT (1) EBRT+HIFU (1) EBRT+CT (1) BT+HIFU (1) MT (1)	Gracilis flap (37) Gluteal flap (1) Singapore flap (1)	16
Elliot et al, ⁶⁶ 2006	6	Transanal (1) Abdominal (1) Perineal (4)	EBRT+ CT (1) EBRT+TA (1) BT+EBRT (3) BT (1)	Dartos flap (1)	16

Abbreviations: CT, cryotherapy; MT, microwave therapy.

patients reported the incontinence as having a significant impact on QOL.

A similar study evaluated QOL in 25 patients following successful transperineal repair with gracilis muscle flap interposition for complex RUF.⁷⁸ RUF cause was radical prostatectomy in 8 (32%), radical prostatectomy plus EBRT in 8 (32%), EBRT plus BT in 4 (16%), EBRT alone in 3 (12%), and cryotherapy in 2 (8%). The patients completed a questionnaire concerning QOL, addressing urine and bowel function. Postoperative urinary continence was reported in 13 (52%) patients. An additional 5 (20%) patients required an AUS for a total of 18 (72%) reporting urinary continence. Regarding bowel function, 2 (8%) reported fecal incontinence, with 1 patient requiring neuro-modulation and an artificial bowel sphincter. Three patients (12%) underwent permanent bladder and bowel diversion with an Indiana pouch and permanent colostomy. Although these two studies were of complex RUF of several different causes including radiation therapy for prostate cancer, the long-term success as gauged through QOL questionnaires of transperineal repair with gracilis muscle interposition was high. There are limited studies to conclude that RUF secondary to radiation therapy should be repaired with a specific approach. Nonetheless, the perineal approach

with gracilis interposition seems to have a high success of fistula closure as well as acceptable post-operative QOL concerning bowel and urinary function.

SUMMARY

Radiation-induced injury of the urinary tract is a complex issue that can lead to debilitating morbidity for the patient. Because of the small number of studies available addressing urethral stricture, BNC, and RUF, a consensus on the management and treatment algorithm has yet to be determined. Nonetheless, available studies indicate that successful reconstruction of these complex lower urinary tract injuries after radiation therapy can be performed.

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Penile Prosthesis Insertion for Acute Priapism

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KEYWORDS

• Priapism • Penile prosthesis • Priapistic episode

KEY POINTS

- Shunt surgery is not universally successful toward detumescence, may lead to erectile dysfunction, and can make eventual penile prosthesis insertion difficult.
- Penile prosthesis insertion during a priapistic episode alleviates ischemic pain, allows the patient to resume sexual function sooner, and prevents corporal scarring and shortening that makes subsequent prosthesis implantation difficult.

INTRODUCTION

Priapism is defined as a full or partial erection that continues more than 4 hours beyond sexual stimulation and orgasm or is unrelated to sexual stimulation. Two broad, cause-derived categories guide management strategies. Ischemic (or veno-occlusive, low-flow) priapism warrants immediate intervention, whereas nonischemic (arterial, high-flow) priapism does not.

The erection in ischemic priapism is marked by profound, unremitting venous congestion that creates a compartment syndrome that ultimately prevents arterial inflow. Corporal blood gas studies have shown that ischemia and acidosis can occur within 6 hours of a priapism episode.¹ Although erectile dysfunction rates approach 25% to 50% in patients with ischemic priapism, those with an episode greater than 24 hours typically face invasive shunt procedures, prolonged pain, and a 90% risk of subsequent erectile dysfunction.²⁻⁴

The delayed sequelae of prolonged ischemia and acidosis frequently result in corporal fibrosis and penile shortening. Therefore, placement of the prosthesis in the acute setting is easier than delayed implantation.³ In patients with prolonged episodes of acute priapism, early implantation

alleviates ischemic pain, allows the patient to resume sexual function sooner, and prevents the corporal scarring and shortening that makes subsequent prosthesis implantation difficult.

PATIENT EVALUATION OVERVIEW

When the persistent erection is accompanied by pain, ischemia should be suspected, because nonischemic priapism is generally not painful. A careful history may reveal predisposing factors, such as sickle cell hemoglobinopathy (or other hematologic conditions), neurologic disease, or pharmacologic reasons for the erection. Pelvic and perineal trauma can result in nonischemic priapism.

On physical examination, inspection and palpation reveal rigid corpora cavernosa, with soft corpus spongiosum and glans tissues. Laboratory testing can detect hematologic abnormalities, and in African American men without a known history of sickle cell disease, a sickle cell preparation and hemoglobin electrophoresis should be obtained. Corporal blood gas analysis can differentiate ischemic from nonischemic priapism, with ischemic blood revealing acidosis, hypercarbia, and hypoxia.

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PHARMACOLOGIC TREATMENT OPTIONS

Initial therapy involves corporal aspiration, irrigation, and injection of α -adrenergic agonists, with the intent of relaxing the smooth muscle and re-establishing arterial inflow, venous drainage, and subsequent detumescence. This approach is highly effective, especially in cases of less than 24 hours' duration.^{5,6}

When priapism is not effectively treated in a prompt manner, irreversible fibrosis develops. Thus, up to 25% of patients with priapism experience chronic erectile dysfunction.⁷ Irreversible fibrotic changes occurring after 48 hours stem from smooth muscle cell necrosis within the corpora cavernosa and subsequent transformation into fibroblastlike cells.^{8,9} The corporal scarring is irreversible and leads to permanent erectile dysfunction that is refractory to medical management and renders delayed surgical placement of a penile prosthesis technically challenging.

SURGICAL TREATMENT OPTIONS

For priapism that is refractory to medical management, corpora-spongiosal shunts are usually performed.^{10,11} There is no general consensus on the management of refractory or delayed cases of ischemic priapism. Immediate insertion of a penile prosthesis is an emerging, effective therapeutic concept in the urological armamentarium.

HISTORICAL PERSPECTIVE ON PROSTHETIC IMPLANTATION

Most initial reports and series for prosthetic insertion for priapism have involved patients with sickle cell trait, delayed and/or recurrent presentation, or failure of previous shunt surgeries. Early reports describe the use of semirigid devices, which were theoretically superior to inflatable devices due to the need to overcome significant corporal rigidity.^{12,13} Surgeons encounter technical challenges with the procedure because of the fibrosis, necessitating corporal tunneling and excavation, with high risk for further interventions.¹⁴

EARLY IMPLANTATION

In 1996, Monga and colleagues¹⁵ introduced the concept of managing potency and recurrence in sickle cell patients with "early" implantation. Rees and colleagues¹ effectively managed 8 patients with ischemic priapism of a mean duration of 91 hours with the insertion of either malleable or inflatable devices. Four (50%) of the patients had failed previous shunts. Only one failure was reported, with penile deformity caused by

compression of an inflatable cylinder by fibrosis, leading the authors to conclude that a semirigid device was best used as a temporizing measure, thereby preserving penile length and corporal patency until an inflatable device can be offered.

COMPLICATIONS

Immediate implantation of a penile prosthesis is not without its risks. In one series, infections occurred in 6%.¹⁶ In the same series, 12% underwent elective exchange for inflatable penile prosthesis; other revision procedures were needed in 12%, and 6% had impending distal erosion of the malleable device requiring replacement with an inflatable device. An important factor in outcomes is the use of surgical interventions before device implantation. It is accepted that ischemic priapism that does not respond to medical therapy should be treated with a shunt, and the 2003 American Urological Association Guidelines recommend reserving shunt procedures until after an adequate attempt to treat with sympathomimetic injections.¹⁷ By compromising corporal integrity, such interventions may expose patients to increased risk of complications, from the shunt procedure itself or if immediate prosthetic insertion is offered.

Apical shunts for ischemic priapism would seem to increase the risk of apical perforation during corporal dilation and subsequent prosthesis extrusion. However, in a series of 12 patients who presented with prolonged ischemic priapism, 11 of whom had undergone unsuccessful shunt surgery, Salem and Aasser reported successful immediate insertion of malleable prostheses in all patients, with only one unilateral corporal perforation that was managed intraoperatively.² They avoided distal protrusion by fixing the cylinders to the edges of the tunicae albuginea with nonabsorbable sling sutures at the site of the corporotomy. With a mean follow-up of 15 months, all patients were satisfied and there were no distal erosions noted. Sedigh and colleagues³ reported 5 patients who had failed distal shunt surgery and underwent immediate insertion of inflatable devices, and all patients had acceptable outcomes. All 5 experienced a decrease in penile sensitivity that resolved at 3 months, and all were satisfied with the results of surgery based on International Index of Erectile Function Questionnaire-5 answers (mean value of 4).

TIMING OF SURGERY

There is no consensus on appropriate timing of penile prosthesis insertion, and one must weigh this factor carefully given the irreversible nature

of the therapy. Most authors agree that irreversible corporal damage occurs within 24 to 48 hours of ischemic priapism, with eventual, unavoidable erectile dysfunction. Immediate insertion of a penile prosthesis should be discussed with these patients, given the benefits to sexual function, penile length, and surgical technique. Some authors suggest a delay of 1 week to appropriately counsel patients and allow for better understanding, but the delay should not exceed 20 days, as the patients who delayed experienced an average penile shortening of 3.5 cm due to severe fibrosis, and the implantations were significantly more difficult.³

Moreover, one may question the need for shunt altogether in select cases. Shunt surgery, although an integral component of the treatment algorithm, has a high failure rate with long-term consequences. Nixon and colleagues¹⁸ found that nearly 50% of patients undergoing initial shunt surgery required additional procedures to achieve detumescence, with 90% reporting significant erectile dysfunction. In patients with prior episodes of erectile dysfunction or medical comorbidity, such as sickle cell disease, failure of aspiration and irrigation may warrant prosthetic placement, given the recurrent nature of the disease process.¹⁹ Conversely, the authors have observed that the long corporotomies performed during acute insertion of prosthetic cylinders function impressively

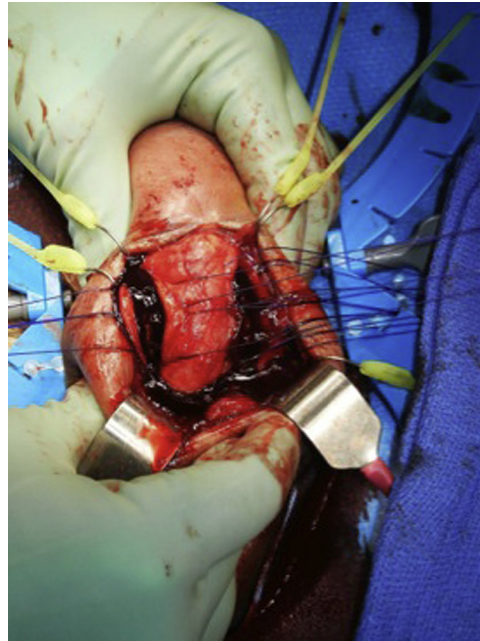


Fig. 2. Removal of old clot.

as an immediate surgical shunt, leading promptly to healthy arterial inflow.

SURGICAL TECHNIQUE

A 2-in longitudinal penoscrotal incision is made—this is longer than the incision normally used for penile implant insertion because a longer corporotomy is required to insert the prosthesis. Patients with ischemic priapism often have significant edema of the penile skin, from both the disease process and the efforts of corporal irrigation. An incision in the scrotum instead of on the penis avoids the edematous penile skin and is a less apparent scar. Blunt dissection is performed

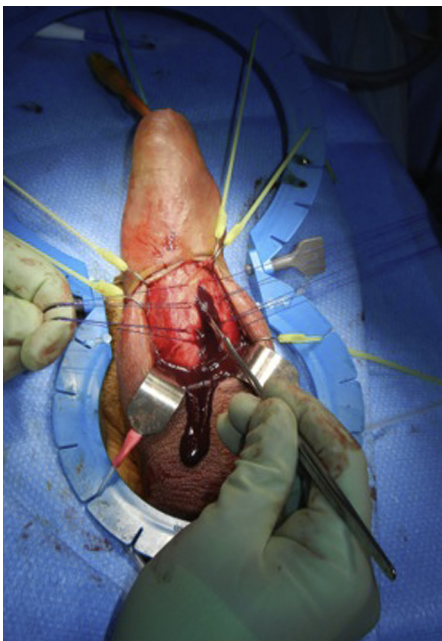


Fig. 1. Incision of corporal cavernosa with outflow of ischemic blood.



Fig. 3. Arterial blood return.

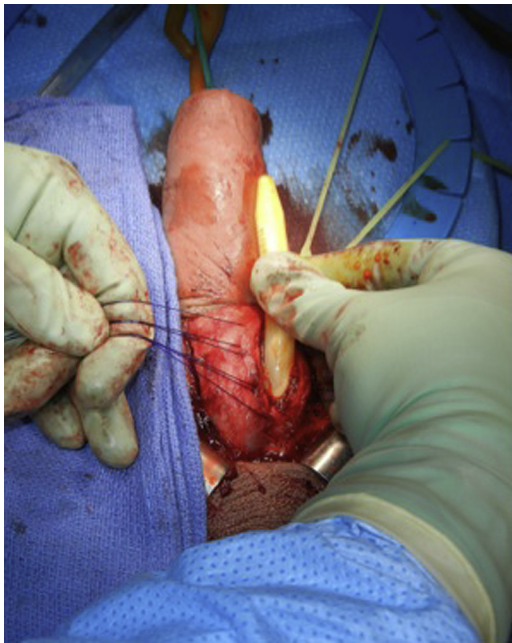


Fig. 4. Placement of malleable penile prosthesis—note that the device is deliberately undersized by 1 cm, extending only to the coronal sulcus.

to reveal the corporal bodies. A self-retaining ring retractor system is used for exposure. Traction sutures with 2-0 polydioxanone are placed on the corporal bodies—the authors use 3 paired traction sutures on each corpora. An incision is made on the corpora (Fig. 1), with return of clotted blood.

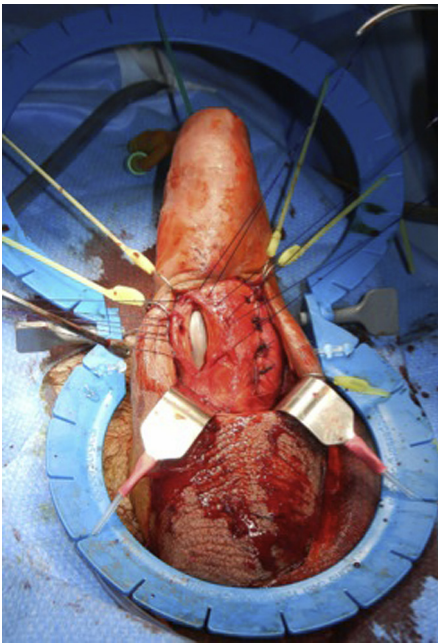
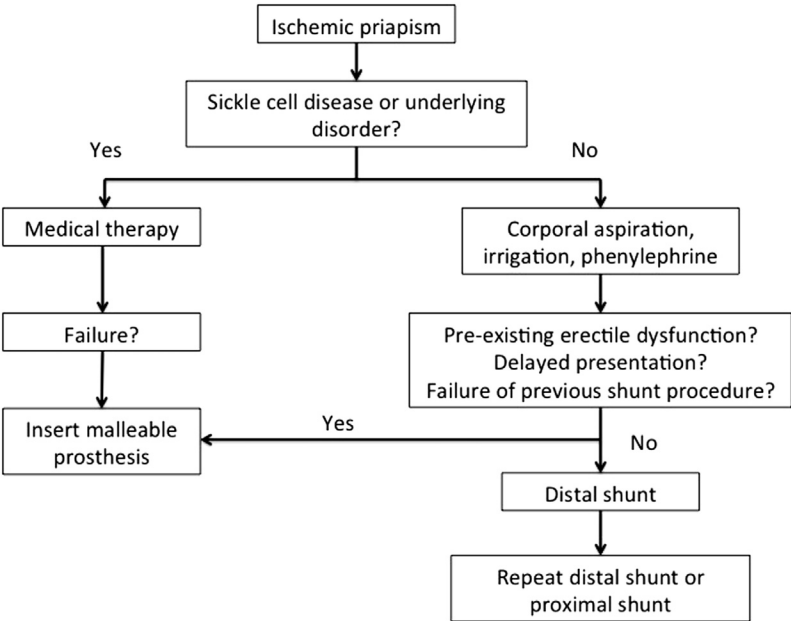


Fig. 5. Corporotomy closure.

Manual compression of the penis may be performed to remove the clot (Fig. 2). Corporal dilation is performed, being especially careful if a shunt had been performed distally. Dilation results in the return of bright red, arterial, blood flow (Fig. 3). The corporotomies and wound are irrigated with antibiotic irrigation. A semirigid penile prosthesis is placed (Fig. 4)—it is essential not to



Management algorithm for acute ischemic priapism.

size the cylinder length aggressively as one would normally do for inflatable device insertion; the authors measure the corporal length only to the coronal sulcus, deliberately undersizing by 1 cm. Traction sutures are then tied together to close the corporotomy (**Fig. 5**). The authors often prefer a 9-mm cylinder diameter in many cases because of the potential difficulty closing the corporotomy due to surrounding congestion and fibrosis. The incision is closed in multiple layers with absorbable suture. It is the authors' practice not to leave drains.

SUMMARY

A reasonable option for treatment of prolonged or refractory ischemic priapism is early implantation of a penile prosthesis, with the advantages of preservation of sexual function, prevention of penile shortening, and relative procedural ease. Timing of the procedure is controversial and warrants careful patient counseling regarding the risks, benefits, level of motivation for subsequent sexual activity, and expectations of any treatment decision.

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Advances in Diagnosis and Management of Genital Injuries

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KEYWORDS

• Genital • Penile • Scrotal • Testicular • Injuries • Trauma • Amputation • Burn

KEY POINTS

- External genital trauma is uncommon and rarely life-threatening but warrants prompt evaluation for proper management.
- The treating physician should have a high index of suspicion when evaluating genital trauma.
- A missed diagnosis can lead to undue, long-term morbidity.
- The treating physician should be selective in obtaining imaging studies based on mechanism of injury and presenting symptoms.
- The primary goal of reconstructive surgery is to preserve tissue, cosmesis, and function.

INTRODUCTION

External genital trauma is uncommon but can cause devastating long-term physical, psychological, and functional quality-of-life consequences. Therefore, the treating physician must be able to diagnose the injury in a timely fashion and be knowledgeable of principles of delayed reconstruction. In the civilian population, genital trauma is roughly 45% penetrating, 45% blunt, and 10% burns and industrial accidents.¹ The most important objective of management is preserving genital function and cosmesis, while minimizing long-term sequelae.

GENITAL AND PERINEAL BURNS

Burns of the genitalia and perineum require referral to a burn center, are rarely isolated, and typically involve other areas of the body. The genitalia alone only comprise 1% of total body surface area (TBSA), and studies have demonstrated an average TBSA of 21% to 56% for all patients with perineal burns.^{2–4} Initial management of perineal burns is removal of all clothing, rapid and

aggressive fluid and electrolyte replacement, and Foley or suprapubic tube placement to monitor sufficient urine output. Evaluation includes a complete physical examination, laboratory evaluation with urinalysis, tetanus prophylaxis, intravenous antibiotics, and an estimate of extent and depth of the burn (TBSA) involved. Burns should be treated according to the mechanism of injury and depth of injury.¹ Genital burns demand very close observation and admission to an intensive care unit or burn unit.

BURN CLASSIFICATION/DEPTH OF BURN

First-degree burns affect the epidermis only and are characterized by pink color, with minimal histologic damage, but significant pain. First-degree burns usually do not have long-term scarring. Second-degree burns are divided into superficial partial thickness and deep partial thickness. Superficial partial-thickness burns involve the epidermis and the papillary dermis and present as pink, moist, tender skin with thin-walled blisters. Deep partial-thickness burns include the reticular

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dermis and present with mottled red and blanched white skin with thick-walled blisters and tender skin. Third-degree burns are full-thickness burns that destroy the epidermis and the entirety of the dermis. Third-degree burns are characterized by a waxy-white or black, dry skin that is insensate.⁵

THERMAL BURNS

Thermal burns of the genitals are caused mainly by flame, but also by boiling water or grease (with scald). Genital burns are typically first-degree and second-degree burns that can be treated without debridement and require only a topical antimicrobial ointment, usually 1% silver sulfadiazine. Genital third-degree burns should be treated with prompt surgical intervention, as conservative management only leads to increased incidence of infection, longer recovery time and hospital stays, and burn scar contracture.

Third-degree burns to the scrotum should be promptly débrided of all nonviable tissue and then immediately skin grafted. With immediate treatment, infection is usually not an issue and there is no reason for delay in scrotal reconstruction with thigh pouch creation.

The penile skin is very thin and thus vulnerable to full-thickness, third-degree burns. Should this occur, the nonviable skin should be sharply débrided; the wound should be primarily closed, and skin should be grafted to the denuded site (Fig. 1). For circumferential penile injury, severe lymphatic obstruction and lymphedema can occur, so all skin distal from the injury site to the subcorona should be excised. Owing to the tremendous vascularity, burns to the glans usually do not need debridement unless it is clearly necrotic.⁶ Patients with third-degree burns to the



Fig. 1. Third-degree genital burn to the penis, scrotum, and inner thigh with meshed split-thickness grafts to cover the denuded area.

glans or the ventral shaft of the penis should have suprapubic tubes rather than Foley catheters. Foley catheters can cause pressure necrosis, resulting in severe hypospadias due to anterior urethral slough, especially when left in a dependent position.

Thermal burns have the potential for long-term sequelae by urethral slough, urethral stenosis, and eventually scar contracture at 3 to 6 months postinjury. These wounds are managed with surgical release and skin grafts.

CHEMICAL BURNS

Chemical burns should be managed with immediate removal of any clothing and aggressive flushing with copious amounts of sterile water. However, do not peel off adherent clothing. Duration of exposure and concentration of the chemical are directly proportional to the extent of the injury. Searching for neutralizing agent is not necessary, as time is of the essence for these patients; most are best served with sterile water irrigation.

ELECTRICAL BURNS

Electrical burns can be devastating, as the degree and the depth of the burn can be deceiving. The damage is often beyond what is obviously visible on the surface and an extensive exploration of the deep and surrounding structures are warranted to evaluate the extent of the injury. A thorough workup for electrical burns include examination for any related bladder, rectum, pelvic organ, or skeletal damage by cystoscopy, sigmoidoscopy, vaginal speculum examination (if applicable), and pelvic radiograph. Urinalysis must be obtained for hemoglobinuria and myoglobinuria, as their presence can cause acute renal damage. When present, management should include aggressive hydration along with urine alkalization. Moreover, as cardiac arrhythmias and arrests have been known to be caused by electrical injuries, cardiac monitoring is also warranted. These burns can be managed in the same manner as a thermal burn, with prompt debridement, primary wound closure, and skin grafting. However, these burns are unique in needing additional debridement, often because of the extended damage. With serial debridements, these wounds can be eventually covered with skin grafts, without additional complications. At times, the debridement can be extensive, and bone or major vasculature is exposed in the wound. Myocutaneous flaps for coverage may be necessary at that point.

ANIMAL AND HUMAN BITES

Animal bites to the external genitalia are rare. Dog bites are the most common cause of injury and children are the most common victims. Initial management should include copious irrigation with saline and providone-iodine solution, debridement, broad spectrum antibiotic prophylaxis, tetanus-rabies immunizations (when appropriate), and immediate/early closure of wound. Infections after dog bites are rare, but treatment is sought soon after the event.⁷ Recommended antibiotic therapies include β -lactam antibiotics with β -lactamase inhibitor (eg, amoxicillin-clavulanate), second-generation cephalosporins (eg, cefotetan, cefoxitin), or clindamycin with fluoroquinolones.⁸

Most human bite victims seek medical care after substantial delay and are more likely to present with gross infection of their wound than with a dog bite. Human bites are contaminated wounds that should never be closed primarily. Empiric antibiotic therapy of choice includes amoxicillin-clavulanate or moxifloxacin.⁹

SCROTAL DEGLOVING INJURIES

Due to the pendulous nature of the male genitalia and the laxity of the covering skin, the scrotum has tremendous capacity to resist injury. The skin, however, remains vulnerable to degloving injuries (**Fig. 2**). In the past, most degloving injuries were caused by agricultural ("power takeoff") and manufacturing machinery, but the incidence has decreased considerably with improved safety measures. Most present-day genital skin avulsion is due to motorcycle or bicycle accidents.

Avulsion injuries are usually along the fascial planes, often torn free without damage to the underlying tunica vaginalis or dartos fascia.¹⁰ The scrotal skin is very compliant, redundant, and

elastic and so defects with up to even 60% skin loss can be primarily closed.¹¹ To help prevent scrotal bleeding/hematoma after injury, a 2-layered closure of the deep fascia and skin is performed with an interlocking, running, absorbable suture. A scrotal drain after repair is controversial because resultant scrotal hematomas are usually in the interstitium of the skin and are not hematoceles.¹² However, if hemostasis is not possible or the patient has a coagulopathy, either a Penrose drain or a closed suction drain (eg, a Blake drain) is recommended. An antibacterial gauze dressing, such as xeroform, with fluff gauze and a compressive scrotal support should be placed to promote comfort and to facilitate healing.

If blunt traumatic scrotal skin loss is extensive (greater than 60%), several options are available for coverage. Repair should be performed without delay if the injury to the scrotum is not contaminated. Local skin flaps are all preferred options for coverage. When additional coverage is needed, split thickness skin grafting is the repair of choice, because it yields excellent cosmetic and functional outcome (**Fig. 3**).¹³ Other ancillary measures include autologous skin grafts and tissue expanders. To begin the procedure, the testicles and cords are sutured together in the midline with multiple 3-0 polyglactin (Vicryl; Ethicon, Somerville, NJ, USA) sutures to create a singular structure, to ease skin grafting. The thick split-thickness skin graft is then harvested with a dermatome at 15 to 18

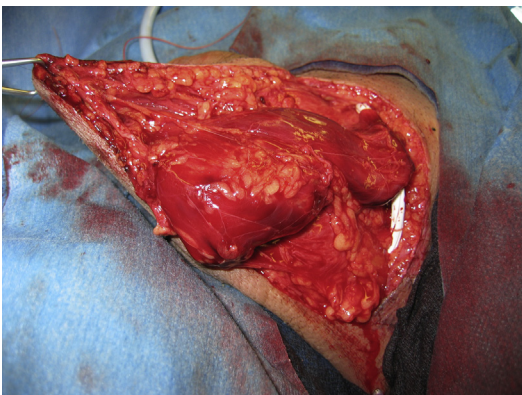


Fig. 2. Extensive scrotal skin loss following a degloving injury.

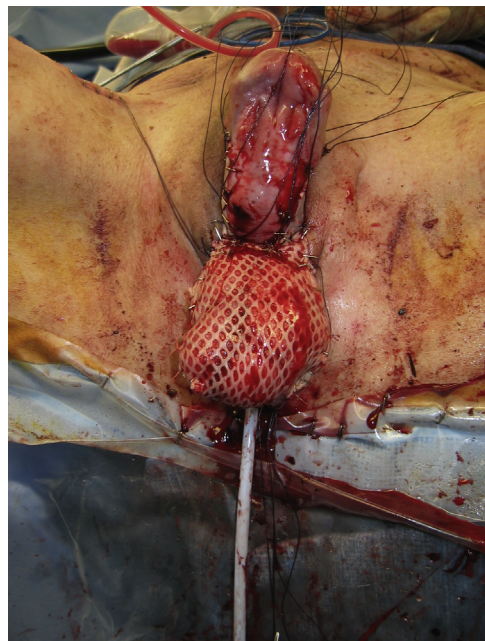


Fig. 3. Meshed split-thickness skin graft to cover the scrotum.

thousandths of an inch, ideally from the inner thigh, and meshed 1.5:1. Skin grafts to the penis are typically performed with nonmeshed grafts for both cosmesis and erectile function. For the scrotum, meshed grafts are used as the meshing simulates rugae, while allowing exudates to escape, thus improving graft take. The graft is then applied to cover the testes and cords and sutured in place at the perineum and ventral penile base. Multiple interrupted chromic sutures are placed in the graft to “quilt” it to the underlying tissue. The “neoscrotum” is then covered with xeroform, mineral oil-soaked cotton batting, and fluff gauze bandage. Bolster sutures of purple-dyed 2-0 Vicryl are then placed at the graft margins and tied over the dressings to facilitate immobilization. An easier-to-apply and quicker alternative to a bolster dressing is the use of a negative pressure wound therapy device (refer to section Management of Complex Urologic Wounds). Postoperatively, the patient is typically kept on bed rest for 48 hours (to prevent graft movement and allow for maximal imbibitions) and the dressings are removed on postoperative day 5. The patient then showers twice a day with soap and water, using a blow dryer on cool or gently patting the graft or harvest site with a towel to dry the graft.¹²

If the circumstances of the injury prevent immediate repair of the scrotum, the testicle should be wrapped in saline-soaked gauze for protection until surgery.¹⁴ If definitive reconstruction is going to be delayed or the genital and perineal skin defects



Fig. 4. Extensive penile and scrotal skin loss following a degloving injury.

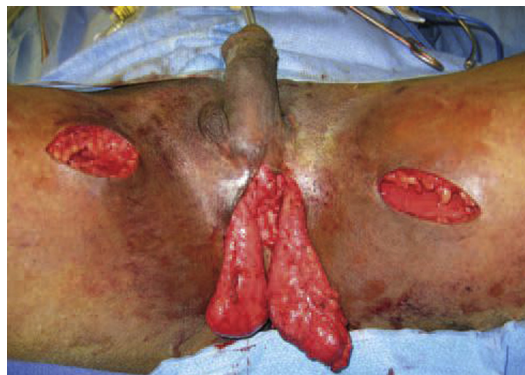


Fig. 5. Creation of testicular thigh pouch following scrotal avulsion injury.

are very large, the testicles may be protected in superficial thigh pouches as long as necessary (Figs. 4 and 5).¹⁵ Thigh pouches not only protect the testes but augment future scrotal reconstruction, reduce the size of the perineal skin defect via secondary intention closure, and lighten the burden of labor-intensive and dressing changes that are often very painful to the patient. Thigh pouches prevent the testes and cord from forming a thick, fibrous, infected rind of granulation tissue. Should this “rind” of granulation tissue form, it must be completely removed down to the spermatic fascia and tunica for skin graft to take. The rind is chronically infected tissue and is a poor bed for skin graft to take. If the rind is left in situ, the neoscrotum becomes contracted and flattened out into an abnormal, nondependent position. Care must be taken to avoid transmission of the infection to the thigh region, so gross contamination must be eliminated beforehand.

To create thigh pouches, the testis and cord are initially dissected to the level of the external ring. To prevent stretching of the spermatic cord with thigh abduction, subcutaneous tissue pockets in the fascia of the thighs should be dissected as far posteriorly and caudally as possible to allow for slack in the cord. Next, the fascia lata of the thigh is identified and then the pouch is dissected superficial to the fascia lata with a sponge stick and 2 narrow deavers into the anterior thigh. If the testes are placed too medially, it may cause pain and discomfort when patients adduct their legs. The plane usually dissects out easily and bluntly. Placing the testes and cord directly on top of the fascia lata facilitates mobilization for delayed scrotal reconstruction.

PENILE DEGLOVING INJURIES

Penile degloving injuries typically require immediate reconstruction and should be treated with a

sense of urgency owing to the nature of their function. Similar to the repair of the scrotum, primary closure of the skin should be attempted. Primary closure of the penis is often difficult, because the shaft skin is not as elastic or as redundant as scrotal skin. Not infrequently, the penile skin defect is circumferential, disrupting distal lymphatic drainage. With circumferential avulsion, the remaining skin distally must be excised to the subcorona to prevent chronic, disfiguring lymphedema.

The primary objective of reconstruction is to preserve erectile function. If a primary closure is not feasible, a thick nonmeshed split-thickness skin graft should be placed because it is less likely to contract (**Fig. 6**). Meshed split-thickness skin grafts on the penis can occasionally contract to the extent that erections become impaired. The skin graft should be wrapped around the penis with the seam on the ventral aspect of the shaft, to simulate a median raphé, while avoiding chordee. (Skin grafts placed on the penis shaft never regain normal sensation. However, sexual function is often preserved due the intact sensation in the glans.¹⁶) The graft is temporarily held in place with staples, and then quilting sutures (interrupted 3-0 chromic suture) are placed. At the proximal and distal aspect of the penis, 4 sutures of long, purple-dyed 2-0 Vicryl are placed circumferentially to tie over a bolster dressing.

The layers of dressing placed on top of the skin graft around the penis are Xeroform gauze, followed by a layer of mineral oil-soaked cotton wadding, fluff gauze, and then a compressive wrap of elastic bandage (conform). The long, purple-dyed stay sutures are then tied down to hold this bolster fixed in place (**Fig. 7**). Postoperatively, the patient is kept at bed rest for 48 hours, and the dressing removed at approximately postoperative day 5. These instructions are then followed by twice-daily showers and gentle drying of the graft with the cool setting of a hair dryer. An alternative, simpler way to immobilize the skin



Fig. 7. "Penis-house" following skin grafting of penis.

graft is to wrap the fluff dressing with elastic bandage (conform) and staple the conform periodically while wrapping it around the penis, leaving the glans exposed. The final tight dressing is stapled at the edges of the skin.

If the patient is impotent and elderly, a meshed split-thickness skin graft is acceptable. In addition, a scrotal flap (modified Cecil technique) can be used to cover the denuded penis, as long as the patient does not mind a hair-bearing penis and is impotent.¹² To create the scrotal flap, a transverse incision is made in the inferior aspect of the scrotum followed by the formation of a subdartos tunnel. The penis is then mobilized through the tunnel, leaving only the glans exposed, while covering the denuded penile shaft. The scrotal flap edge is then sutured to the subcoronal skin

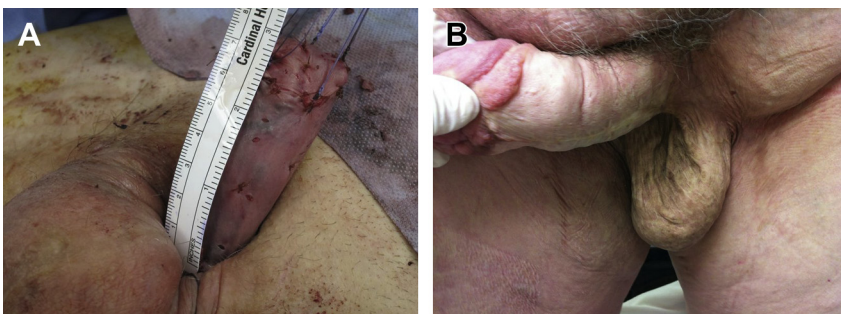


Fig. 6. (A) A thick nonmeshed split-thickness skin graft around the shaft of the penis. (B) Two months postoperative following penile skin grafting.

with interrupted absorbable sutures. Patients have the option to undergo a second-stage repair to free the penis, which few select.

PENILE FRACTURE

Fracture of the penis is a tear of the tunica albuginea of the corpus cavernosum, frequently while the penis is rigid and erect. When erect, the tunica albuginea stretches and thins to 0.25- to 0.5-mm-thick, compared with 2-mm-thick when flaccid.¹⁷⁻²⁰ Thus, the erect penis is more prone to serious injury (axial rupture) than the pendulous, flaccid penis during blunt trauma. In the Western Hemisphere, the most common cause of fracture is vigorous vaginal intercourse, most commonly when the woman is on top and the penis is acutely bent.^{21,22} In the Middle East, however, the most common cause of fracture is self-penile manipulation in an attempt to achieve rapid detumescence.²³ Classically, signs and symptoms of penile fracture are a snapping or “popping” sound, followed by rapid detumescence, severe pain, ecchymosis, and swelling of the damaged side, with deviation away from the damaged side.^{24,25} Typically, the penile fracture is a transverse corporal tear on the ventral portion of the penis, close to the urethra (**Fig. 8**). Many patients present in a delayed fashion because of embarrassment. The incidence of penile fracture is higher than prior reports, as some develop minor corporal tears, but never seek medical care.

Penile fracture is a clinical diagnosis. Imaging is not needed, particularly when the patient presents with a convincing history and physical examination.¹² Despite that there are numerous reports of the accuracy of cavernosography and magnetic resonance imaging to diagnose penile fractures, such methods are too invasive, time consuming, or costly to justify, particularly when the diagnosis can be made clinically.¹⁹ Although sexual trauma

can also lead to the rupture of the dorsal vein of the penis and mimic penile fracture, the use of diagnostic imaging should be highly selective (**Fig. 9**). In contrast, if urethral injury is suspected, retrograde urethrography or flexible cystoscopy must be performed. Urethral injury has been reported in 10% to 38% of penile fracture cases.¹⁰ Any signs of urethral injury, such as difficulty voiding, blood at the urethral meatus, or any degree of hematuria, should cause a high index of suspicion in the physician and deserve further evaluation.

Immediate surgical repair is the treatment of choice for penile fracture, as low complication rates and good outcomes have been reported by numerous centers.¹² Although conservative management may be an option in patients with minor tears of the tunica albuginea, most untreated fractures will develop delayed and persistent penile pain or curvature with erection. However, Kozacioglu and colleagues²⁶ have looked at delayed versus immediate repair and concluded that delayed repair had no ill effect as a consequence of a delay in surgery in patients without urethral involvement. Neither serious deformities nor erectile dysfunction was seen in the long term for these patients who had delayed repair. Although penile fracture is treated as a surgical emergency, from a practical view, waiting until the next morning for repair seems reasonable.

Surgical repair of the fracture requires exposure of the defect in the corpora cavernosum and gross inspection of the urethra, given the 20% rate of associated urethral injury.¹² Depending on the location of the injury, the options for exposure include a circumferential, subcoronal, degloving incision of the penile skin or a longitudinal incision directly over the injury exposing only the tunical tear. At first, the hematoma should be evacuated, and the fracture site washed out. If the location of



Fig. 8. Penile fracture with urethral tear.

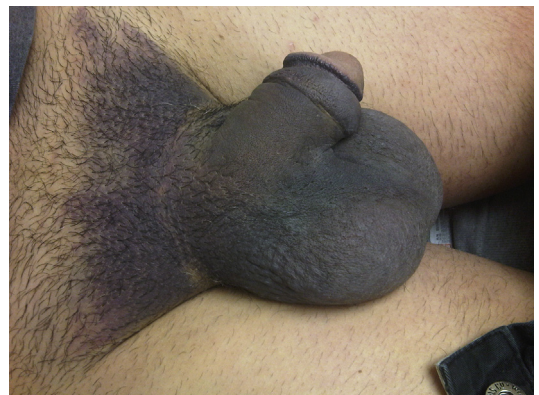


Fig. 9. Superficial dorsal vein rupture imitating penile fracture.

the corporal tear is not clear, a Penrose tourniquet can be placed at the penile base with a butterfly needle placed into the corporal shaft and injected with saline (as in a Gittes test). Extravasating saline usually helps identify the location of the defect. Primary closure of the corpora is usually performed using a running absorbable suture (2-0 Vicryl).

Complete urethral disruptions should be reanastomosed without delay, with the ends debrided, spatulated, and reapproximated tension-free over a urethral catheter. If there is a partial tear of the urethra, then a "stenting" urethral catheter can be placed with a suprapubic tube, but primary repair of the tear should be performed when possible. Pericatheter urethrography is performed after 2 to 3 weeks after the procedure to confirm urethral healing before catheter removal.

TESTICULAR RUPTURE

A testicular rupture is a tear of the tunica albuginea with extrusion of seminiferous tubules (**Fig. 10**). Although both penetrating and blunt mechanisms can cause testicular rupture, most are blunt. The age group most vulnerable to testicular rupture is 10- to -30-year-old men and boys involved in sports-associated activity or motor vehicle accidents.²⁷ In all cases of blunt scrotal trauma, the physician should have a high index of suspicion and the rupture ruled out. Clinical examination can be rather difficult in these patients because many present with severe pain and swelling.

Although all penetrating injuries deep to the scrotal dartos fascia should be surgically explored, not all blunt injuries require exploration. Many physicians will conservatively manage injuries that do not show clinical or radiological

evidence of rupture. Scrotal ultrasonography, in the hands of a skilled sonographer, can serve as a vital addition to the physical examination, particularly if examination findings are equivocal.²⁸⁻³¹ The sonographic findings are a heterogeneous echo pattern of the testicular parenchyma with loss of contour of the testis tunica (100% sensitivity and 93.5% specificity).³² Injuries that are clinically benign and homogeneously echogenic on ultrasound do not require surgical exploration.

In all cases of testicular rupture, urgent surgical exploration is essential for salvage of the testicle.¹² Although testis rupture is not life threatening, it can have numerous repercussions including infertility, hypogonadism, and low self-esteem. The surgeon should attempt to salvage/preserve any remaining viable tubules, as studies have revealed reduced endocrine abnormalities and improved semen quality compared with orchiectomy.^{33,34} Blunt ruptured testes explored within 72 hours have a salvage rate of greater than 90%, whereas those explored late have a 45% salvage rate.³⁵

To achieve maximal exposure to both testes and cords in addition to maintaining cosmesis, the scrotum is typically explored through a vertical incision of the median raphe. The tunica vaginalis is then opened and the testis is brought out of the scrotum and the testicle is inspected for injury. Any nonviable seminiferous tubules are then sharply excised and any hematoma is drained, leaving only healthy bleeding edges. The tunica albuginea is then closed, using a running 3-0 absorbable suture (**Fig. 11**). The testis is returned into the scrotum, with the lateral groove of the testis oriented properly to prevent torsion, and the scrotum is closed in 2 layers with absorbable sutures. A Penrose or closed suction drain can be placed through a separate stab incision if hemostasis is a concern. The wound is protected with fluff gauze



Fig. 10. Close-up view of testis rupture with extrusion of seminiferous tubules.



Fig. 11. Closure of tunica albuginea following testis rupture.

and held in place with a scrotal support for compression. Anti-inflammatory medications, ice packs, and scrotal elevation may limit postoperative edema and hasten convalescence.

PENETRATING WOUNDS

Penetrating trauma to the genitalia is rare. Most cases are gunshot wounds (GSW) but stab wounds make up a significant portion. Although military GSW are from high-velocity weapons with significant injuries, most civilian GSW reported are from low-velocity weapons, causing less acute and delayed tissue damage.³⁶ All patients with penetrating penile wounds require a retrograde urethrography or urethroscopy, because up to 50% have an associated urethral injury.^{37–39}

Early surgical exploration, debridement, and primary repair of penetrating injuries are the preferred management for both the penis and the testes.⁴⁰ Repair of a penetrating penile wound is comparable to that of a penile fracture. Depending on the location, direct visualization of the corpora can be obtained via a circumferential, degloving, subcoronal incision or via a penoscrotal, infrapubic, or perineal incision for more extensive wounds.¹² For minor injuries to the corpora, primary closure is adequate, as it is done for penile fractures.

Repair of testicular injury from a penetrating trauma also follows the same principles as that from a rupture from a blunt injury. Approximately 50% of GSW to the scrotum strike the testis and, of these, one-half of the testes are viable for repair.¹² Much like testicular rupture, salvage of viable testicular tissue is the primary goal of management. After debridement of the nonviable tissue, the tunica albuginea is closed primarily. In cases where the defect is wide and there is a deficiency of tunica albuginea to close primarily, a free graft of tunica vaginalis is used to cover the defect and preserve the testicle.⁴¹ A tunica vaginalis graft can be easily harvested and sewn to the edges of the tunica albuginea for coverage (Fig. 12). Synthetic grafts (ie, Gore-Tex) result in poor outcomes secondary to infection and eventual orchiectomy. Thus, using the native tunica vaginalis tissue is the optimal tissue for coverage, and a clear alternative to orchiectomy.¹²

PENILE AMPUTATION

Traumatic genital amputations are usually self-mutilations performed by acutely psychotic patients or transsexuals unable to have (afford) sexual reassignment surgery.^{42–47} A multidisciplinary team of urologists, plastic surgeons, psychiatrists, and social workers is needed to care

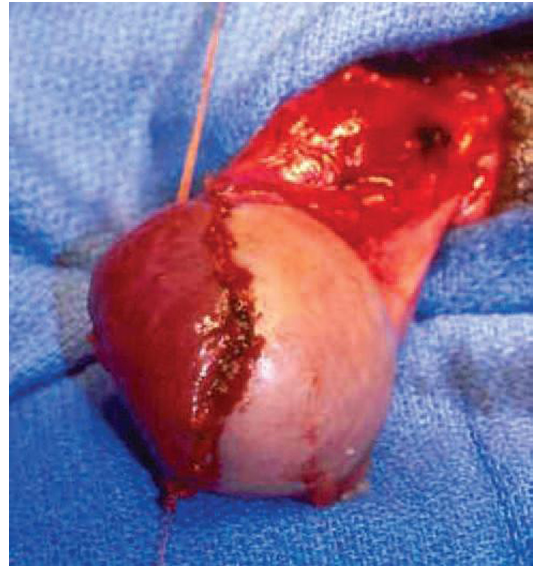


Fig. 12. Testicle after successful graft with tunica vaginalis.

for the penile amputation patient properly. Less commonly, genital amputations are caused by agricultural and industrial machinery accidents.⁴⁸ Of note, the largest series of reanastomosis of penile amputations was reported in Thailand.⁴⁹ During the 1970s, there were an estimated 100 penile amputations by angry wives against their philandering husbands, with 18 cases replanted at the same medical center.

There are 3 options to treat the amputated penis, depending on the degree of damage: closure of the residual stump, surgical reanastomosis of the amputated penis, or total phallic substitution with reconstruction regardless of the psychological state of the patient. Once the psychotic episode is properly treated, most patients are very remorseful of self-amputation. If the amputated penis is viable, penile reanastomosis should always be attempted. The amputated penis should be thoroughly washed out and debrided with either normal saline or lactated Ringer solution and then cooled in a “double bag.”⁵⁰ The “double-bag” technique involves wrapping the amputated penis in saline-soaked gauze and then placing it in a first sterile sealed bag. Next, the first bag is placed in a second bag or basin of ice-slush. This maneuver protects the penile skin from direct contact with ice while still maintaining a hypothermic state, optimally at 4°C. Penile replantation is attempted up to 24 hours after the injury because success has been reported after 16 hours of cold ischemia and 6 hours of warm ischemia.^{51,52}

The patient should be stabilized, with aggressive fluid resuscitation and blood transfusion

as indicated.⁴⁵ Whenever feasible, the patient should be cared for at a center that has the capability of performing microvascular surgery by a specialist.^{44,46} Microvascular reattachment has shown superior outcomes with decreased skin necrosis and glans slough, improved sensation, and superior function when compared with macrovascular technique. If a patient cannot be treated at a center with microvascular capabilities, then a macrovascular reattachment can be attempted. This reattachment is certainly suboptimal, for the reasons stated above, but is a better option than defaulting to a penile stump.

To begin replantation, vascular control is obtained at the base of the proximal cut edge of the corpora. Local compression with gauze or tourniquet may be required depending on the extent of the hemorrhage. After controlled hemostasis, the tunica albuginea of the corpora cavernosa should be reapproximated with interrupted 3-0 polyglactin (Vicryl) suture. Placement of several sutures through the intercavernous septum will provide stabilization. The central cavernosal arteries do not need to be reanastomosed, because it does not improve outcome. The proximal and distal urethral edges are then mobilized for about 1 cm with the ends spatulated. Next, the urethra is reanastomosed over a 16-French silicone Foley catheter with interrupted 5-0 or 6-0 polydioxanone (Maxon, United States Surgical Corporation, Norwalk, CT, USA or PDS, Ethicon, Somerville, NJ, USA) suture in a single layer. Placement of a suprapubic tube is recommended to divert the urine proximally to facilitate healing.¹²

Once the penis is stabilized, then the deep dorsal vein is microscopically re-anastomosed with 11-0 nylon or polypropylene (Prolene, Ethicon, Somerville, NJ, USA). This anastomosis is critical and must be patent to prevent corporal edema, swelling, and subsequent ischemia. Next, at least one, preferably both, of the dorsal penile arteries are reapproximated in an end-to-end fashion, which immediately re-establishes blood flow to the subcutaneous tissues and prevents postoperative skin necrosis. Last, as many nerve fibers as can be identified are then reapproximated with a simple nylon or polypropylene suture in the epineurium. Dopplerable blood flow through the dorsal arteries needs to be confirmed before completing the case.¹²

If penile skin is intact, the skin edges are either reapproximated with interrupted 4-0 chromic sutures or a thick, nonmeshed, split-thickness skin graft is placed when the penile skin is unusable or denuded. A last resort and less attractive method of coverage is to bury the penis in a subcutaneous tunnel in the scrotum (using a modified

Cecil technique), which leads to a suboptimal hair-bearing, thick-skinned penile shaft, which may require additional surgery.¹⁰ It is crucial to cover the vascular anastomoses to avoid delayed thrombosis and necrosis and replantation failure. Finally, the penis is wrapped in loose dressings and an external splint is fashioned vertically to facilitate venous and lymphatic drainage.

If penile replantation is not an option because of loss of the detached penis or damaged beyond repair, then the penile stump can be closed as done for a standard elective partial penectomy (Fig. 13). The neomatus is widely spatulated to prevent stenosis. A free forearm phalloplasty can be performed subsequently.

Postoperative management must include at least 48 hours of bed rest and perioperative broad-spectrum antibiotics. The Foley catheter can be removed after at least 3 weeks of stenting, following a pericatheter retrograde urethrogram or a voiding cystourethrogram, which verifies a healed anastomosis. The suprapubic tube is capped and then removed after a few days of normal voiding. In cases of self-mutilation, the patient's mental health must be addressed and closely monitored and the psychiatry department must be involved with this patient's care.

TESTIS AMPUTATION

Although the penis, if properly cooled, can be successfully replanted, the testes are much more delicate and cannot tolerate extended periods of warm ischemia. Due to their highly metabolic state, the testes have only a 4- to 6-hour period following amputation for successful replantation.¹⁰ If the patient is at risk for hypogonadal state, as with an atrophic or absent contralateral testis, microvascular technique is recommended for the best possible outcome.



Fig. 13. Urethra mobilized for spatulation following penile amputation.

First, the 2 edges of the spermatic cord are debrided and the spermatic veins, the spermatic artery, and the vas deferens must be identified within both ends. The spermatic artery is anastomosed together using an 11-0 nylon or Prolene suture under microscopic view. If performed properly, the spermatic veins will begin to bleed on the testicular side and can be easily identified. If technically feasible, then at least 2 veins should be joined together with their severed counterparts. Last, the vas deferens must be realigned via a vasovasostomy in an end-to-end fashion performed in a 2-layer fashion, connecting first the vaginal mucosa using 10-0 nylon or Prolene suture. The vaginal muscularis is reapproximated using 9-0 nylon or Prolene suture, and then the spermatic fascia is closed primarily. To protect and support the fragile anastomoses, an orchiopexy is performed to secure the testicle in place. If the native scrotal skin is viable, the scrotum should be closed primarily over the reattached testis. Conversely, if more than 60% of the scrotal skin is absent, then the replanted testicles should be placed in thigh pouches until a neoscrotum is reconstructed, in the method described earlier for scrotal avulsion.

In all cases of self-inflicted genital amputation, patients must be closely observed following replantation surgery. Psychiatry must be closely engaged in these patients' care, because they are likely to repeat their actions if not properly managed.

MANAGEMENT OF COMPLEX UROLOGIC WOUNDS

Many traumatic wounds are difficult to manage despite optimal care. At times, the wound defect may be so large or complex that reconstruction is not feasible. Negative pressure wound therapy (NPWT) is not a new concept in wound therapy; it was first reported by Fleischmann and colleagues⁵³ in 1993. An NPWT device (VAC Therapy; Kinetic Concepts, Inc, San Antonio, TX, USA) is used to create a negative pressure over the wound, which drains the excessive interstitial edema, decompresses small vessels, and restores local blood flow. Other benefits of NPWT include reduction of bacterial colonization and stimulation granulation tissue growth to promote wound closure. To set up an NPWT, a piece of foam is placed over the wound with a large piece of transparent tape cover and a drain tube is set to transport fluid to a vacuum pump. Any open wound can be converted into a controlled closed wound with an NPWT device.

An NPWT may be used for many types of wounds, including dehiscent surgical wounds,

complex operative wounds left open to heal by secondary intention, meshed skin grafts and flaps, stage III and IV pressure ulcers, chronic open wounds, diabetic foot ulcers, venous stasis ulcers, degloving injuries, and partial-thickness and full-thickness burns (<12 hours of burn). It should not be used for patients with malignancy, necrotic tissue that has not been debrided, fistulae to body cavities/organs, untreated osteomyelitis, wounds with bleeding bed, or patients on anticoagulation therapy.⁵⁴

In 2005, Armstrong and colleagues⁵⁵ enrolled 162 patients with complex wounds after a partial foot amputation into a 16-week, multicenter, randomized, clinical trial. Seventy-seven patients were randomly assigned to NPWT with dressing changes every 48 hours versus 85 control patients who received standard moist wound care according to consensus guidelines. NPWT was delivered through the vacuum-assisted closure therapy system. Wounds were treated until healing or completion of the 112-day period of active treatment. This study showed that the NPWT group healed more than the control group (43 [56%] vs 33 [39%], $P = .040$). The time to complete wound closure was also faster in the NPWT group than in controls ($P = .005$). In addition, the rate of granulation tissue formation was faster in the NPWT group than in controls ($P = .002$).

The costs of NPWT are significant, and this has discouraged many clinicians from using the therapy. However, there are reports showing the faster healing time with NPWT compared with conventional therapies correlating to decreased overall cost of care.⁵⁶ Philbeck and colleagues showed that the average wound closure rate with an NPWT (vacuum-assisted closure) was 0.23 cm²/d, compared with 0.09 cm²/d for a wound treated with saline-soaked gauze. The average 22.2-cm² wound in the study took 247 days to heal at a cost of \$23,465 with saline-soaked gauze versus 97 days to heal at a cost of \$14,546 with an NPWT system. The study showed that the NPWT is an efficacious and economical therapy option for variety of chronic wounds.

NPWT combines the benefit of both open-wound and closed-wound treatment. NPWT is not universally applicable to all type of wounds, however. In a carefully selected patient, it can serve as a practical addition to the traditional wound therapy options available to the reconstructive surgeon.

SUMMARY

Traumatic genital injury predominantly affects the young and is usually not life threatening.

Nevertheless, the treating physician must have a high index of suspicion when evaluating genital injuries. Although missed diagnosis can result in dire consequence with life-long sequelae, rapid and proper treatment can help preserve tissue, cosmesis, and function.

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Skin Grafting of the Penis

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KEYWORDS

• Penile reconstruction • Skin grafting • Penile lymphedema • Penile trauma • Fournier gangrene

KEY POINTS

- Choice of reconstruction of penile skin loss depends on anatomic and functional factors.
- Normal skin graft healing involves imbibition, inosculation, and revascularization.
- The most common causes of skin graft loss are hematoma, seroma, infection, or shear.
- Skin grafting of the penis can be challenging because of the ability of the penis to change size.

INTRODUCTION

Penile skin loss may occur after a variety of disease processes. Reconstructive options are tailored to the defect. When skin is missing, skin grafting can achieve the goal of reconstructing like with like.

Even urologists who do not specialize in reconstruction may be called on to give their advice in complex cases, especially after necrotizing genital infections. Although they are experts in general reconstructive principles, plastic surgeons may not be aware of the unique anatomic and functional factors in penile and genital reconstruction; collaborative efforts are often necessary.

INDICATIONS FOR PENILE SKIN GRAFTING

Several disease processes may cause actual or functional loss of penile skin, and skin grafting is often necessary to reconstruct these wounds. The most common problems include necrotizing infections of genital skin (ie, Fournier gangrene), lichen sclerosus, trauma, and burns. Resection of penile cancer or genital lymphedema may require removal of skin from the penis, leading to a need for replacement. A circumcision sometimes results in too much skin removal and the need for a skin

graft. In addition, reoperative repair of hypospadias or penile urethral stricture may use oral mucosal or skin grafting.

SKIN ANATOMY

Skin has many roles, most importantly serving as a barrier to the outside world. The skin has 3 layers: the epidermis, the dermis, and the hypodermis or subcutaneous layer (**Fig. 1**). The epidermis, the most superficial layer, produces and maintains the stratum corneum, the waterproof outermost barrier of the skin. The epidermis also contains important specialized cells such as melanocytes, immune cells, and sensory cells.

The dermis makes up the remaining 90% to 95% of the total skin thickness and provides a collagen matrix to support the epidermis. The skin appendages, such as hair follicles, sweat glands, and sebaceous glands are found in the dermis. The hair follicle has multipotent bulb cells that are important in reepithelialization of a wound.^{1,2}

TERMINOLOGY

A skin graft is skin that is removed from one anatomic location, without a blood supply, and

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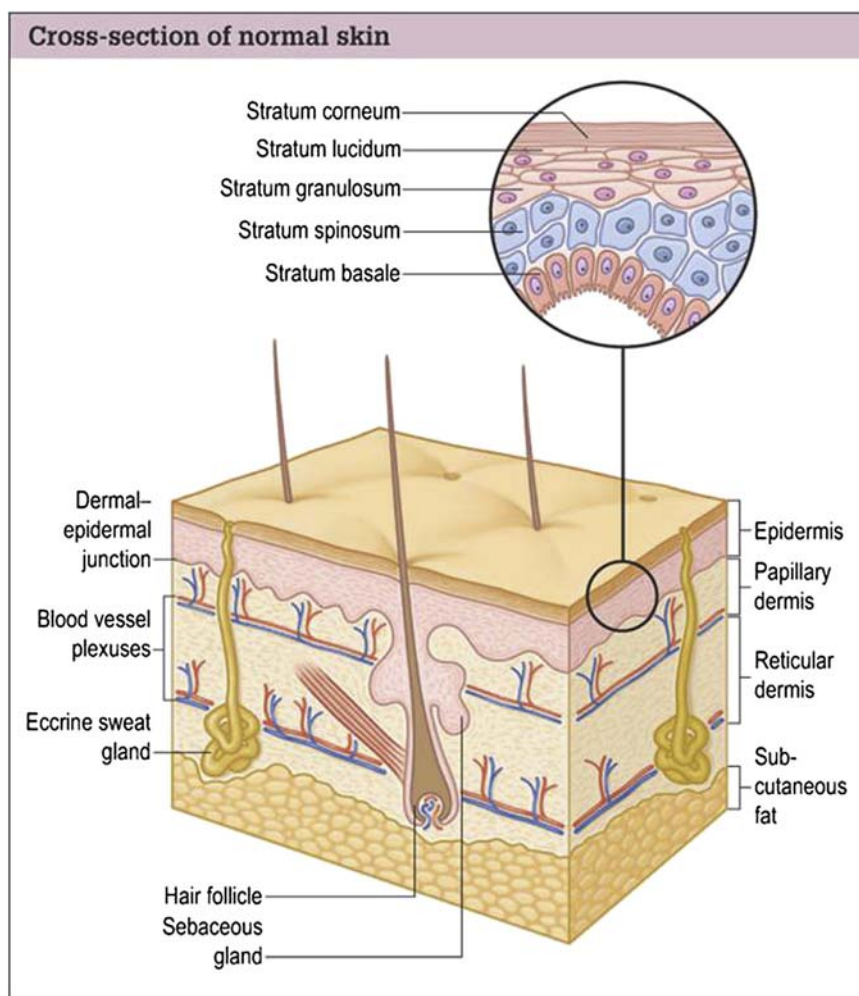


Fig. 1. Layers of the skin. (From Fang RC, Mustoe TA. Structure and function of the skin. In: Guyuron B, Eriksson E, Persing JA, editors. Plastic surgery: indications and practice. Philadelphia: Saunders Elsevier; 2009; with permission.)

transplanted to a new site. Engraftment is the process of revascularization and healing of the graft. Skin grafts are commonly categorized in terms of the depth of the graft. A full-thickness skin graft is comprised of all the dermis and epidermis. This graft is harvested at the interface of the dermis and hypodermis (see Fig. 1). The thickness of this graft is determined by the anatomic site from which it is harvested. For example, a full-thickness skin graft obtained from the prepuce is thinner than a graft harvested from the back. In the case of a full-thickness skin graft, the donor site is closed primarily. In contrast, a split-thickness skin graft comprises the epidermis and only a portion of the dermis. It is harvested with a dermatome, an instrument that shaves a sheet of skin of controlled width and thickness.

DIFFERENCES BETWEEN SPLIT-THICKNESS AND FULL-THICKNESS SKIN GRAFTS

There is more dermis in a full-thickness skin graft than in a split-thickness skin graft, so there are some important distinctions in the behavior and potential use of both types of grafts (Table 1). Because split-thickness skin grafts are thinner and have less tissue, they have less metabolic demand from the wound bed, and thus have better survival or take. In contrast, a full-thickness skin graft is thicker and, as such, has greater metabolic demand. Survival of a full-thickness skin graft is more uncertain and it requires a well-vascularized recipient site.

Full-thickness skin grafts display significantly more primary contraction than split-thickness

Table 1
Characteristics of full-thickness and split-thickness skin grafts

	Full-thickness Skin Graft	Split-thickness Skin Graft
Amount of dermis	More	Less
Primary contracture	More	Less
Secondary contracture	Less	More
Metabolic activity	More	Less
Hair growth	More	Less
Sweat gland function	More	Less
Sebaceous gland function	More	Less
Sensory return	More	Less

skin grafts. Primary contraction is the recoil that occurs immediately after a skin graft is harvested and is directly related to the amount of elastin present in the dermis. A full-thickness skin graft can lose up to 40% of its surface area from primary contraction. These rates are lower with grafts that have less dermis. For example, a thin split-thickness skin graft only loses 10% of its surface area from primary contraction.³

Over time, full-thickness skin grafts have a tendency to resist the significant problem of secondary contraction, the contraction of a skin graft after healing. Myofibroblasts within the graft are primarily responsible for secondary contraction. The use of thicker skin grafts, with more dermis, helps to prevent this type of contraction. Once secondary contraction ends, full-thickness skin grafts tend to stretch and grow with an individual, whereas split-thickness skin grafts tend not to expand as well.³

Another important distinction between full-thickness skin grafts and split-thickness skin grafts is the durability of the graft. Once again, this difference is directly related to the thickness of the dermal layer. Thicker grafts are better able to resist friction and trauma.

It is also notable that the skin's appendages, such as sweat and sebaceous glands, are present in the dermis. As such, full-thickness skin grafts have a greater ability to sweat or produce oil. However, this ability depends on the reinnervation of the glands, which can take several months to years. In the interim, it is important to keep skin

grafts well moisturized to prevent drying, which can lead to fissuring of the grafted skin, especially for split-thickness skin grafts, which are lacking in these glands permanently.

Hair follicles are also present in the dermis, and full-thickness skin grafts show the hair growth pattern of the donor site. It is therefore important to make sure that full-thickness skin grafts used in penile reconstruction are obtained from a hairless area. Split-thickness skin grafts are generally hairless and thus are generally preferred on the penis.

In choosing a skin graft, donor site morbidity must also be considered. A full-thickness graft, by definition, leaves a full-thickness defect at the donor site, and large donor sites may be difficult to close or hide. Split-thickness grafts have the benefit of leaving a donor site that heals with only simple wound care. In addition, the thickness of dermis varies by anatomic site and with age. The dermis is thinner in children and with advancing age,⁴ and what may be a thick split-thickness graft in a young adult patient may leave a full-thickness wound in the elderly.

CHOICE OF SKIN GRAFT IN PENILE RECONSTRUCTION

The choice of graft thickness depends on the needs of the wound to be covered and the inherent compromises associated with graft thickness. A core principle of reconstructing tissue loss is to replace like with like, meaning choosing donor tissue that most closely replicates the native tissue in function and appearance. The skin of the penis is thin, hairless, and flexible. Because of the dramatic change in size of the penis with erection and the need for durability because of the tissue demands of sexual activity, full-thickness skin grafts seem to be the preferred choice in the replacement of penile skin. Although some prefer full-thickness grafts in penile skin replacement,⁵ in most cases it is best replaced by a split-thickness skin graft (Fig. 2).^{6,7} A thick split-thickness skin graft offers the best combination of graft take and durability.

In some cases, a full-thickness skin graft may be appropriate in penile reconstruction. The most common example is in urethral reconstruction. Although a detailed discussion of graft urethroplasty is outside the scope of this review, understanding the principles behind graft selection and the factors that determine success is essential. Urethral reconstruction calls for tissue that resists the stress of urine passage. At present, a full-thickness oral mucosal graft is the closest replacement tissue for the urethra. It is used extensively in staged reconstruction of urethral repairs and

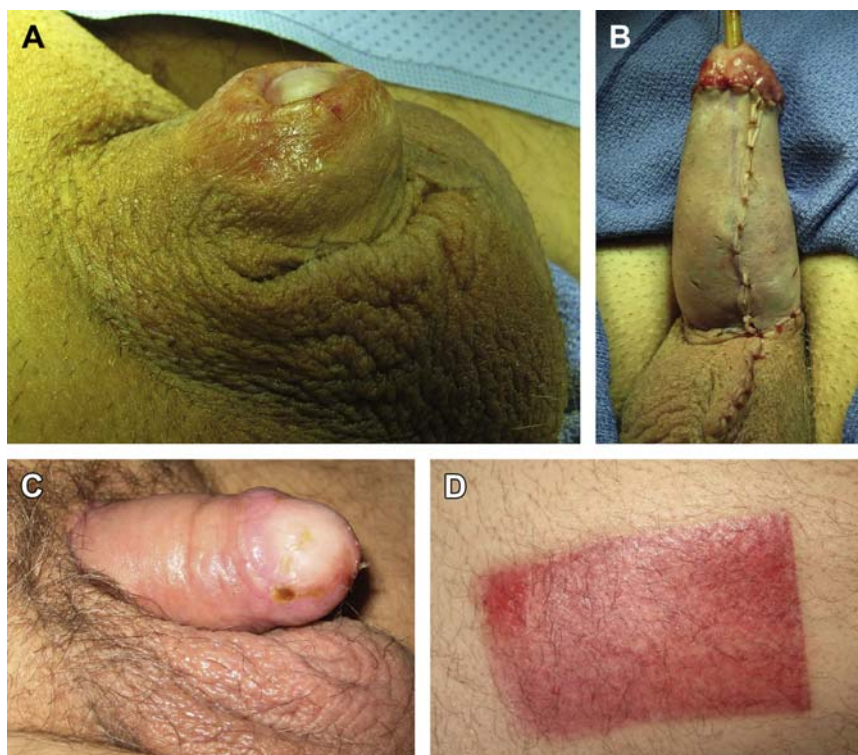


Fig. 2. (A) Patient with skin loss and buried penis from lichen sclerosus. (B) Patient after excision of scarred skin and split-thickness skin grafting to penis. (C) Patient 5 weeks after surgery. (D) Lateral thigh skin graft donor site 5 weeks after surgery.

complex hypospadias.⁸ Meshed foreskin and split-thickness skin grafts used in staged urethral reconstruction⁹ have fallen from favor, especially as oral mucosal grafts have come into use. In some circumstances, the prepuce of an uncircumcised patient may be used to reconstruct penile skin elsewhere.

NORMAL SKIN GRAFT HEALING

Engraftment involves removing tissue (skin or mucosa) from its native location and blood supply and transferring it to a recipient bed, where the transplanted tissue undergoes revascularization. Disruption of this process leads to graft failure.

The first phase of engraftment is known as plasmatic imbibition and lasts for 24 to 48 hours. During this time, the diffusion of nutrients, oxygen, and metabolic waste occurs passively back and forth across the concentration gradient from the graft to the wound bed.¹⁰ For the duration of the imbibition phase, the graft is without blood flow and appears white. Greater vascularity of the wound bed results in shorter graft ischemia time. Because it is composed of more tissue and has

greater metabolic demand, a full-thickness skin graft can only tolerate this ischemia for about 3 days. However, a split-thickness skin graft is more forgiving because it has less metabolic demand. It can survive ischemia through imbibition for up to 5 days.¹¹

The next stage, inosculation, begins within 36 hours and involves the formation of anastomotic connections between host and graft vasculature. Skin grafts begin to have capillary refill during this phase. As blood flow begins, it is disorganized at first. As such, especially full-thickness skin grafts may appear slightly cyanotic at this time.¹²

During the final phase of skin graft healing, revascularization, new vessels within the graft establish the definitive vasculature that will ensure the long-term survival of the graft. Whether the preexisting vessels in the graft act as conduits for ingrowth and become reendothelialized, or entirely new vessels form, or all of these occur, remains an area of ongoing research.¹³

Over time, it is normal for skin grafts to become hyperpigmented or hypopigmented. Grafts that are harvested from the lower trunk and thighs have a tendency to darken or take on a yellow

color as the graft matures, especially with skin grafts from the groin. Thinner skin grafts have a greater tendency to be hyperpigmented.^{14,15}

Skin grafts can reinnervate over time. The process of nerve ingrowth begins both from the wound bed and from the periphery of the skin graft, progressing inwards.¹⁶ This process can take more than 2 years. The extent of reinnervation depends on the presence of neurilemmal sheaths within the graft. The more dermis that is present in the graft, the better the likelihood of reinnervation. Thus, full-thickness skin grafts have better potential for reinnervation than thin split-thickness skin grafts.¹⁶

ABNORMAL SKIN GRAFT HEALING

Adverse local factors and errors in surgical technique can lead to graft failure. The most common cause of graft failure is fluid accumulation under the graft. Hematoma or seroma formation between the graft and recipient bed increases the distance required for diffusion of nutrients during the imbibition phase. In addition, a hematoma can create a barrier between the graft and the wound bed, inhibiting revascularization.¹⁷ Careful hemostasis is important to prevent this complication.

The second most common cause of skin graft failure is infection. Atraumatic graft handling and a well-vascularized and clean wound bed are paramount. Skin graft survival is improved when there are fewer than 10^5 colony-forming units of bacteria per gram of tissue.¹⁸ Fibrin has a bacteriostatic effect and has an important role in the survival of skin grafts.¹⁹

Additional causes of graft failure include moving of the graft, or shearing. Shearing disrupts the neovascularization from the host bed to the graft. Quilting sutures may be placed to decrease the dead space between the graft and the recipient bed and to decrease shear injury.¹⁷ The graft will fail any place where the graft is not in direct contact with the wound bed. Bolster or negative-pressure wound dressings can also help in this regard by helping to hold the graft in place on the wound bed.

TECHNIQUE OF SPLIT-THICKNESS SKIN GRAFTING

The first step in reconstruction after penile skin loss is preparing the wound bed. In cases of necrotizing genital infections, debridement of all necrotic tissues may take one or many surgical procedures. Once the wound bed is healthy, and the patient has been stabilized, reconstruction of the wound can proceed. Broad-spectrum

antibiotics are administered before surgery. A urinary catheter is placed. The penile shaft and tunica vaginalis are good recipient graft beds, and the presence of granulation tissue is not necessary for skin graft coverage. The wound bed is debrided to decrease bacterial contamination.

Thick split-thickness skin grafts are preferred for replacement of the penile shaft skin. The dimensions of a wound may not be apparent until the penis is put on stretch or an erection is induced. At the least, the penis should be placed on stretch through the use of a glans suture when measuring to determine the necessary skin graft. Because of primary contraction, the size of the graft taken should be larger than the penile defect by approximately 20%. A split-thickness graft harvested for coverage of most locations may typically be 0.03 mm (0.0012 inch). For the penis, a thicker graft of 0.04 mm (0.0016 inch), with its associated greater amount of dermis, is better able to resist the friction and wear of sexual activity, and is elastic enough to stretch with erections.

The hair over the donor site is removed. The lateral thigh is generally used as a donor site because it can easily be draped within the area of the wound, and it is easy to procure a wide (75–100 mm [3–4 inch]) sheet graft from this area. In addition, compared with the medial thigh, the lateral thigh is less sensitive. The patient is asked before surgery regarding his preference as to which side to use, in an attempt to avoid harvesting from the side on which the patient sleeps. If the lateral thigh cannot be used, the abdominal wall, buttocks, or back can make suitable, but less convenient, donor sites. Some investigators advocate harvesting a split-thickness graft from the skin resected when treating genital lymphedema²⁰; however, when skin is grossly abnormal it should be discarded.

The donor site is lubricated. Mineral oil is often used, but we prefer the use of chlorhexidine gluconate solution 4.0% because it is easier to remove and does not interfere with adhesive dressings. The donor skin is made taught with the aid of an assistant to help in procuring the graft. Next, the skin graft is obtained with a pneumatic or electric dermatome, such as a Zimmer (Zimmer, Warsaw, IN) or Padgett dermatome (Integra, Plainsboro, NJ). The donor site is then temporarily dressed with Telfa gauze (Covidien, Mansfield, MA) soaked in saline with epinephrine to help with hemostasis. A local anesthetic is injected to help with postoperative pain because the donor site is especially uncomfortable.

Creating an outlet for the egress of fluid is important in preventing hematomas or seromas. Meshing is a technique for providing drainage from

beneath the graft. The graft is passed through a mesher on a plastic carrier that determines the expansion ratio. We typically mesh and expand grafts to the scrotum by 1:1.5. Meshing has the added benefit of allowing the graft to cover a greater surface area (**Fig. 3**). However, expanded meshed grafts yield a netlike scar pattern on healing. In addition, because the interstices heal by secondary intention, there is more contraction of the graft.

In cosmetically sensitive areas and where minimal graft contraction is desired, such as the penis, a nonmeshed graft, or sheet graft, is preferred. Instead of meshing, the pie-crusting technique (**Fig. 4**) allows fluid to drain from beneath a graft. This technique entails creating perforations in the graft with a blade. The perforations are oriented in a random pattern to avoid drawing the eye to any specific pattern.

The skin graft ideally is placed over the penile shaft in such a way that the incision line recreates the median raphe on the ventral surface (**Fig. 5**). The skin graft is sutured to the surrounding skin with 4-0 chromic sutures. Quilting sutures, placed in a manner avoiding the urethra and dorsal neurovascular bundle, should be used to adhere the graft closely to the wound bed to prevent seroma or shear. If the glans has been deepithelialized, as may be the case in patients with lichen sclerosus, skin graft is placed over the denuded area.

Fibrin glue has been shown to slightly improve skin graft take in simple reconstructions. However,



Fig. 3. A split-thickness skin graft has been meshed 1:1.5 and applied to the testicles and perineum.

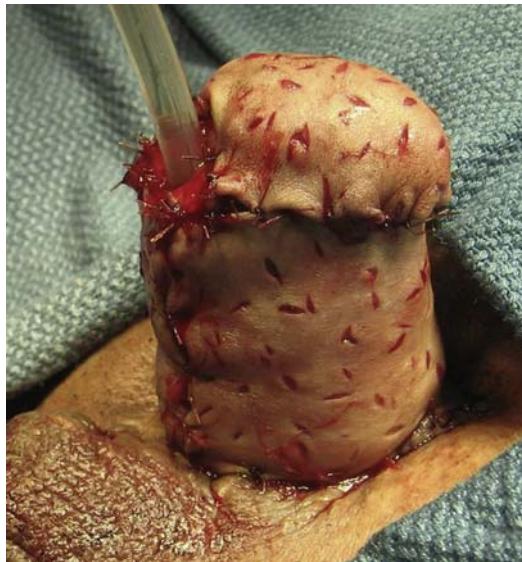


Fig. 4. A patient who had traumatic partial penile amputation and loss of penile skin underwent split-thickness skin grafting with pie-crusting incisions of graft to allow for drainage of blood and serum from beneath the graft.

its real benefit is in difficult areas to graft, such as the penis or perineum. Several studies have found significant improvement in graft take when used in mobile areas or areas close to skin folds.^{21,22} Using a thin layer of diluted fibrin glue may help with graft adhesion²³ and minimize the concern of adding a barrier to imbibition and inosculation.

Often the testes need skin coverage at the same time as the penis, particularly after necrotizing genital infections or lymphedema. The scrotum may be reconstructed with thigh flaps, but we find split-thickness skin grafting of the scrotum to be less morbid and to heal with good cosmetic results, especially when the tunica vaginalis has been preserved. The testes are sutured to one another in the midline. The skin graft is generally taken at 0.03 mm (0.0012 inch) thickness and then meshed in a 1:1.5 ratio (see **Figs. 3** and **5B**). The graft is then sutured to the tunica vaginalis or directly to the tunica albuginea of the testes with 4-0 chromic sutures.

In cases in which only a small area of the penis requires grafting, such as in staged urethral reconstruction, a tie-over bolster dressing is a simple, efficient way of compressing the graft to prevent hematoma or shear. Our preference is to use sterile surgical prep sponges as the bolster on top of petrolatum gauze (**Fig. 6**). Sutures are placed through the adjacent penile skin and tied together over the bolster. The ties should be snug but not so tight as to damage the skin through which the

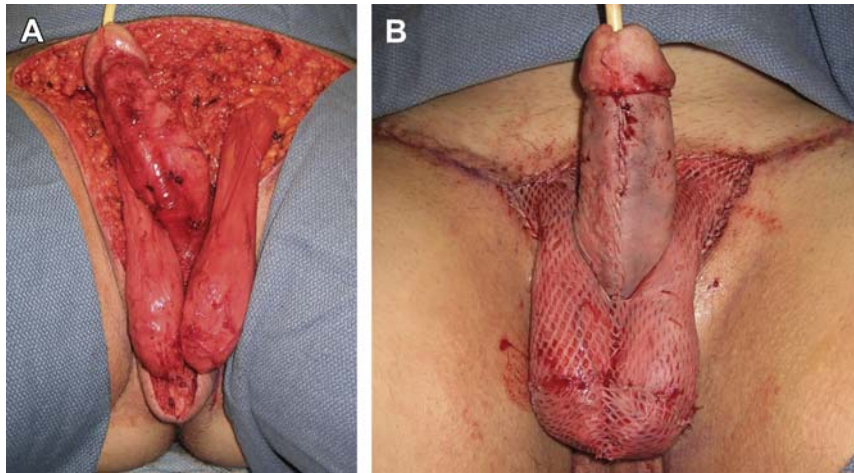


Fig. 5. (A) Perineal and penile wound after debridement of genital lymphedema. (B) Split-thickness skin grafting of the perineum and penis. Note that the penile skin graft has been applied as a sheet graft and has been pie crusted, whereas the perineal skin graft has been applied as a meshed graft. Some portions of the wound have been repaired by primary closure.

suture is placed. A tie-over bolster may even be used in glans reconstruction.²⁴

For circumferential penile skin grafting, our preference is to dress the skin grafted areas with petrolatum gauze and a negative-pressure wound dressing.²⁵ Negative-pressure wound dressings (such as VAC Therapy, Kinetic Concepts, Inc, San Antonio, TX), may help the graft to conform closely to the underlying tissue, thus precluding the accumulation of fluid (Fig. 7A).²⁶ Circumferential negative-pressure dressings on the penis have been shown to be safe and effective in penile skin grafting.²⁷ When applying a negative-pressure wound dressing to the penile shaft, we also apply tongue depressors outside the sponge to help maintain the length of the penis (see Fig. 7B), because the negative-pressure dressing will otherwise not keep the penis stretched to length. The negative-pressure wound dressing is then placed at 100 to 125 mm Hg continuous pressure. However, the negative-pressure dressing alone cannot be relied on to achieve contact between the graft

and the bed, and areas of the graft that are not in direct contact with the recipient bed will necrose.

The dressing and urinary catheter are then left in place for 5 days, during which time the patient is kept on bed rest. After the dressing is removed, antibiotic ointment and petrolatum gauze are used to dress the wound until it has finished healing for the next 2 weeks. After this, the patient is instructed to apply lotion to the grafted areas daily as all skin grafts are without sebaceous gland activity, at least in the early healing period.

The skin graft donor site is covered with a semioclusive dressing such as Tegaderm (3M, St Paul, Minnesota) or Op-Site (Smith & Nephew, St Petersburg, FL). Semioclusive dressings tend to be more comfortable than leaving the wound open or using semiopen dressings such as scarlet red or petrolatum gauze.²⁸ The donor site may collect serous fluid while covered with a semioclusive dressing. This fluid can be aspirated using sterile technique, and the puncture site covered with another semioclusive dressing. If the donor site dressing is leaking, it can be reinforced or removed and petrolatum gauze placed over the donor site. Depending on the thickness of the skin graft, the donor site can take between 7 and 21 days to reepithelialize. Once the donor site has healed, the dressing is removed, and the patient is encouraged to apply lotion to the wound daily.



Fig. 6. A tie-over bolster is used to dress a full-thickness graft in staged urethral reconstruction.

FULL-THICKNESS SKIN GRAFTING IN PENILE RECONSTRUCTION

Oral mucosal grafts are most often used full-thickness skin graft in genital reconstruction and

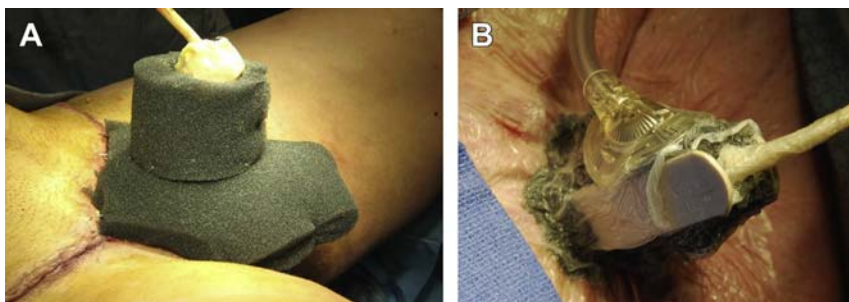


Fig. 7. (A) Negative-pressure wound sponge is placed over the skin graft as a bolster. (B) Negative-pressure wound dressing applied with tongue depressors cut to size outside the sponge to keep the penis to length.

are largely beyond the scope of this discussion. However, the use of full-thickness grafts in staged urethral reconstruction follows the same principles critical for success of split-thickness grafts: careful hemostasis, close apposition to the graft bed, and graft immobilization. Other sources of hairless skin may include abdominal or flank skin in some patients, supraclavicular skin, and postauricular skin. These grafts must be fully defatted to maximize their potential for engraftment. Although usually abundant, scrotal skin is typically not the best choice for penile skin replacement because it is hair bearing.

When harvesting a full-thickness skin graft, the target area is marked. Marking an ellipse 3 times as long as it is wide that includes the target area allows for primary wound closure without lateral wound redundancy. Once harvested, the graft should be defatted so that the dermis is in direct contact with the wound bed. This defatting may be done during the graft harvest, leaving the fat behind as the graft is harvested. As an alternative, the graft may be defatted on the back table. The authors prefer to do this with the graft draped over the surgeon's nondominant index finger, using sharp scissors on the convex surface of the graft (**Fig. 8**).

TIPS IN PENILE SKIN GRAFTING

Surgeons reconstructing penile skin loss after trauma or necrotizing infections must work with what tissue remains; often this means loss of tissue down to the Buck fascia. However, in elective circumstances, such as buried penis caused by lichen sclerosus or genital lymphedema, the surgeon must choose what tissue to resect, and this affects the outcome of the reconstruction. In the resection of penile lymphedema, the skin and dartos layer are removed down to the Buck fascia to prevent recurrence of lymphedema.⁶ In other circumstances, such as surgery for lichen sclerosus, cicatricial and abnormal skin should

be resected leaving the underlying dartos tissue. Because the dartos layer and loose tissue beneath the skin are not tightly affixed to the Buck fascia, grafting on the dartos layer preserves the skin's mobility.

When there is loss of the proximal penile skin, the natural tendency is to preserve any viable distal skin. However, when there is loss of the proximal penile skin, the proximal dartos layer is generally also lost. This loss results in disruption of lymphatic drainage of the distal penile skin. The native skin should be resected to the level of the glans to avoid a ring of lymphedematous skin around the glans (**Fig. 9**). If skin loss is not circumferential, it may be preferable to leave the native skin in place, especially if several days of observation have not led to increasing edema of the skin.

The glans penis is a unique structure where the skin layer is directly attached to the tunica albuginea beneath it. There are few situations in which there is loss of skin of the glans without loss of the underlying spongy tissue. Because the penile shaft skin and glans have separate blood supplies, most cases of penile skin loss do not involve



Fig. 8. A full-thickness graft is defatted. The convex surface of the finger and the oppositely convex curve of the scissors allows precision in where the hypodermis is excised.

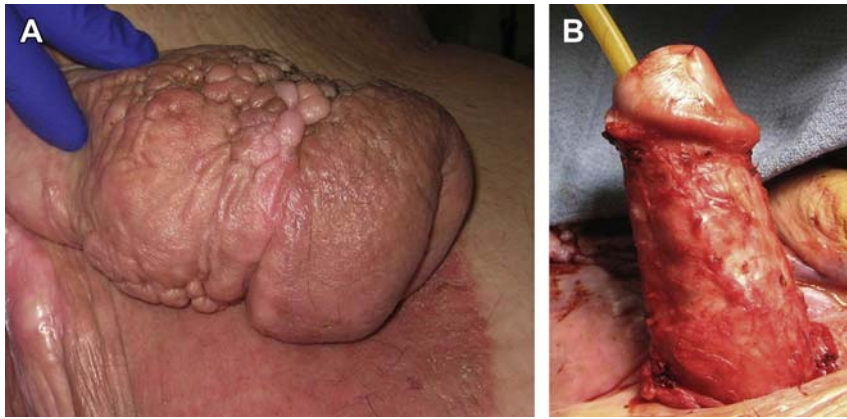


Fig. 9. (A) Patient who underwent meshed split-thickness skin graft to the proximal penile shaft after necrotizing genital infection debridement. The distal shaft skin was left in place, later becoming grossly lymphedematous and enveloping the glans. (B) Same patient after resection of all grafted and native penile skin.

the glans. However, efforts to treat benign and malignant disease in an organ-preserving manner have led to techniques such as glans resurfacing.²⁹ This technique involves removing glans skin and replacing it with a split-thickness skin graft³⁰ or by grafting onto the ends of the corporal bodies after distal penectomy to recreate the appearance of the glans (see **Fig. 3**).³¹

Surgeons have tried to prevent nocturnal erections, a normal occurrence during the rapid-eye movement sleep cycle, after urologic surgery for decades. However, there is little evidence to support success of medical therapies to prevent erections.³² This reemphasizes the need to closely affix the graft to the penis and use a dressing that prevents shear.

SUMMARY

Many disease processes may result in a need for replacement of penile skin. Thick split-thickness grafts are the most appropriate choice for penile skin reconstruction because of the special characteristics of penile skin, namely thin, hairless skin, with stretch capability. Reconstruction of the penile skin can be challenging because of the expanding nature of the penis and difficult contours of the area. Using proper surgical technique and postoperative wound care maximizes graft success.

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Grayscale transrectal ultrasonographic prostate biopsy using local anesthesia remains the standard approach to the definitive diagnosis of prostate cancer. Careful patient evaluation and preparation are essential to maximize the results and minimize the complications of the biopsy procedure.

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Office-Based Stone Management **481**

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As hospital resources are becoming strained, ambulatory surgical centers and day hospitals are being increasingly utilized. For the urologist, a working knowledge of local anesthetics and conscious sedation protocols are important, as many surgical kidney-stone procedures can be performed without general anesthetic. With any anesthesia, the key goal is to maximize patient comfort while minimizing respiratory depression and avoiding prolonged sedation. When using these medications, a working knowledge of emergency reversal, ventilation (bag mask/laryngeal mask airway/intubation), and cardiopulmonary resuscitation is recommended.

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Office-Based Management of Impotence and Peyronie's Disease**521**

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Erectile dysfunction (ED) impacts more than 50% of men older than 40 years; Peyronie disease (PD) affects up to 10% of men, with an adverse impact on normal sexual function and overall well-being. ED can also be the first sign of other underlying disease. The office-based evaluation of ED and PD is the first step in the management of these devastating conditions of men's health. New and exciting nonsurgical therapies are now available to help treat these conditions and restore sexual function and quality of life.

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Kiranpreet K. Khurana and Edmund S. Sabanegh Jr

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Electrical and Mechanical Office-based Neuromodulation**581**

Ravi Kacker, Aaron Lay, and Anurag Das

Overactive bladder (OAB) is commonly encountered in urologic practice. Treatment algorithms begin with conservative therapy and pharmacotherapy with antimuscarinics. Some patients do not receive adequate relief from these methods or they do not tolerate side effects from pharmacotherapy. A test stimulation for sacral neuromodulation and percutaneous tibial nerve stimulation are office-based techniques that are commonly used as the next step in the algorithm of care in patients with OAB. These techniques are efficacious and approved by the Food and Drug Administration for treatment of overactive bladder and its associated symptoms.

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Jennifer Rothschild, Ian M. Thompson III, Raoul S. Concepcion, and Neal D. Shore

The specialty of urology has historically adapted to the changing health care environment. Urologists have been quick to adopt new technology, new therapeutics, and devices to render state-of-the-art patient care with improved clinical outcomes. The busy urology practice is now in the position to deliver many novel and unique therapies across multiple disease states. As a result, clinicians can provide state-of-the-art care in a clinic setting and potentially reduce the overall costs of health care delivery. This article reviews some of these potential new opportunities available to the practicing urologist.

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Martha K. Terris and Zachary Klaassen

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Transrectal Prostate Biopsy

Mohamed T. Ismail, MD^{a,b}, Leonard G. Gomella, MD^{b,*}

KEYWORDS

Prostate cancer Prostate biopsy Detection Diagnosis Transrectal ultrasonography
Technique

KEY POINTS

- Grayscale transrectal ultrasound (TRUS)-guided prostate biopsy using local anesthesia remains the standard approach to the definitive diagnosis of prostate cancer.
- Careful patient evaluation and preparation are essential to maximize the results and minimize the complications of the biopsy procedure.
- Image guided enhancement for prostate biopsy allows for better visualization and their role in the diagnosis is evolving.

INTRODUCTION

Prostate cancer (PCa) is the most common neoplasm in the Western hemisphere, and the incidence is still increasing.¹ Screening, detection, and diagnosis of PCa are currently based on serum prostate-specific antigen (PSA) level; digital rectal examination (DRE) and transrectal ultrasound (TRUS)-guided systemic biopsies. Although there is intense controversy concerning PCa screening, when a decision is made to perform a diagnostic prostate biopsy (PB), TRUS is the preferred and standard-of-care technique.²

TRUS has many advantages over other medical imaging modalities. The lack of ionizing radiation, low cost, and the proximity of the prostate to the rectal wall resulted in TRUS being the most commonly used prostate imaging modality. After the initial introduction of the sextant PB technique proposed by Hodge, little refinement of the technique was carried out until Stamey³ suggested directing the biopsies more laterally. It was then recognized that even lateral sextant biopsies could miss up to 30% of cancers, because more extended biopsy schemes result in higher cancer detection rates.^{4,5} As defined by the National

Comprehensive Cancer Network (NCCN), an extended PB (EPB) is essentially a sextant template with at least 4 additional cores from the lateral peripheral zones as well as biopsies directed to lesions found on palpation or imaging.⁶ Little controversy exists in the urologic community regarding the usefulness of EPB compared with sextant biopsy in increasing the detection rate of PCa.

INDICATIONS

PB is indicated when there is suspicion of advanced or metastatic PCa based on factors such as bony metastasis or pelvic/retroperitoneal adenopathy or suggestive symptoms. More commonly, the decision to perform PB has been traditionally based on abnormal DRE or increased PSA level. Abnormal DRE usually indicates an initial PB irrespective of PSA level. In the Washington PCa screening study,⁷ 14% of the cancers were diagnosed by DRE alone. Among those patients who underwent radical prostatectomy (RP) based on abnormal DRE, 20% were non-organ confined and 20% had a Gleason score of 7 or greater.

Disclosures: The authors have nothing to disclose.

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The debate regarding the pros and cons of PSA-based screening continues and is beyond the scope of this review.^{8,9} If a patient opts for PSA-based screening, there is no absolute cutoff for PB (Table 1). Most sources recommend repeating an abnormal PSA value before making the decision to perform PB with a normal DRE, and there is general agreement that PSA higher than 4 is suggestive of the presence of PCa for a biopsy. A PSA threshold of 2.6 ng/mL doubles cancer detection rates in men younger than 60 years with little loss in specificity.¹⁰ There are several other factors to consider in proceeding to biopsy, potentially including PSA velocity, % free PSA, PSA density (PSAD), age, family history, ethnicity, and comorbidities. The NCCN recommends the use of a PSA velocity of 0.35 ng/mL/y or greater as indication for biopsy in men with PSA 2.5 ng/mL or less.⁶ In addition, the group recommends the use of % free PSA as alternative indication of initial biopsy, with the intention of avoiding unnecessary biopsies. The % free/total PSA ratio can be used to indicate biopsy if less than 10%, consider PB intermediate if between 10% and 25%, and no PB if greater than 25%. PSAD and age-referenced PSA have been investigated but are controversial.⁶ Recent data from the dutasteride REDUCE (reduction by dutasteride of prostate cancer events) chemoprevention trial again confirmed that family history is a significant risk factor for cancer.¹¹ Several researchers found that African American

race remains an independent predictor of PCa detection in men undergoing initial PB.^{12,13}

Newer tests such as kallikrein markers in blood, genomics, proteomics, and a variety of urinary markers such as PCA3 and TMPRSS2-ERG remain under investigation to aid in the decision making for PB.¹⁴ Box 1 lists the factors to be considered as an indication for PB.

Predictive models have been developed to reduce unnecessary biopsies and still detect most clinically important cancers and are available on the Internet. The finasteride-based PCa Prevention Trial model (<http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp>) uses variables such as PSA, age, family history, race, DRE, and previous negative biopsy.¹⁵ The European Randomized Study of Screening for PCa (ERSPC)-based model has several calculators (<http://www.prostatecancer-riskcalculator.com/>) that rely on additional items such as TRUS-estimated prostate volume and the presence of hypoechoic lesions.¹⁶ Other indications for PB include as a part of an active surveillance (AS) protocol¹⁴ and in the evaluation of recurrence after local radiation therapy.¹⁷

PATIENT PREPARATION

A complete history and physical examination, urinalysis and culture, and PSA determination are mandatory before a PB. Attention to any anorectal

Table 1 Summary of some major organizations recommendations for PSA cutoff for initial biopsy		
Organization	PSA Cutoff	Reference
American Urological Association PSA best practice statement: 2009 update	No longer recommending a single cutoff	http://AUAnet.org
NCCN guideline version 2012	PSA $\geq$ 2.5 ng/mL and PSA velocity $\geq$ 0.35 ng/mL/y PSA 2.6–4.0 ng/mL PSA $\geq$ 4.0 ng/mL especially if free PSA $\leq$ 10%	http://www.nccn.org
European Association of Urology guidelines on prostate cancer, 2012 update	No longer recommending a single cutoff For young men, PSA values <2–3 ng/mL are often used	http://www.uroweb.org
National Institute for Health and Clinical Excellence, UK clinical guideline 58, prostate cancer 2008	No longer recommending a single cutoff	http://www.nice.org
Australian Cancer Network Localized prostate cancer: a guide for men and their families in 2010	No longer recommending a single cutoff	http://www.cancer.org.au
Canadian Urological Association PSA screening: The Canadian perspective	No longer recommending a single cutoff	http://www.cua.org

Box 1
Factors to be considered as an indication for PB

DRE
PSA value
PSA velocity
% Free PSA
Family history
Race
PSAD
Comorbidities
Kallikrein markers, genomics, and proteomics
PCA3 and TMPRSS2-ERG

Box 2
Factors to consider before a PB

History and physical examination including DRE
PSA
Urinalysis and culture
Use of oral anticoagulants
Use of antiplatelet medications
Use of a rectal enema

disease that may interfere with the probe or needle insertion should be noted. The use of low-dose aspirin does not seem to increase bleeding and should be continued if deemed medically necessary. Oral anticoagulants should be stopped 5 days before the biopsy and low-molecular-weight heparin bridging used if medically indicated.

The use of rectal enema to reduce infectious complications is contentious, with 81% of urologists in the United States using an enema in preparation for a TRUS biopsy.¹⁸ Several studies showed that the risk of infectious complications is lower if a rectal enema is used.^{19,20} In a large study from Korea, infectious complications developed in 1.3% of patients who had rectal preparation, but in 9.5% of those who did not.²¹ In another nonrandomized Korean study,²² the use of a povidone-iodine suppository before biopsy markedly reduced infectious complications.

However, a study by Carey and Korman²³ reported that enema before biopsy provides no significant advantage in clinical outcome. Moreover, in a recent study from Canada,²⁴ rectal cleansing with povidone-iodine before TRUS biopsy did not significantly reduce the risk of infectious complications. **Box 2** lists the factors to consider before a PB.

ANTIBIOTIC PROPHYLAXIS

Infectious complications associated with TRUS biopsies are a growing concern. More frequent complications are being observed,^{25,26} and the rate of resistance to commonly used antibiotics is increasing.^{27,28} Infectious complications related to TRUS biopsy range from transient fever to urinary tract infection (UTI), sepsis, and possible death. The rate of sepsis after TRUS biopsy is

estimated to be between 0.1% and 5%, with UTIs occurring in 3% to 11% of patients.^{25,26,28,29} The standard of care is to use antibiotics at the time of TRUS biopsy. Traditionally, fluoroquinolones have been used.³⁰ In a survey of more than 900 US urologists,¹⁸ more than 85% reported using fluoroquinolones. There is no evidence whether a single or a more extended protocol is needed. Recent studies suggest that the escalating rates of infectious complications and need for hospitalization are often caused by fluoroquinolone-resistant bacteria.^{25,27,31} Two antibiotic prophylactic strategies are being used (**Box 3**). Studies have shown reduced risk of infection in patients by adding a single dose of aminoglycoside just before biopsy.^{32,33} Another proposed strategy is the use of rectal swabs before TRUS biopsy to screen patients for colonization with fluoroquinolone-resistant bacteria and then to use targeted antimicrobial prophylaxis.^{34,35} The antibiotics for PB recommended by the American Urological Association (AUA) include fluoroquinolones or first-generation/second-generation/third-generation cephalosporins.

Alternatively, aminoglycoside or aztreonam 1 metronidazole or clindamycin may be used. The only agents for which oral administration is acceptable for PB are the quinolones.

ULTRASOUND PROBE CONFIGURATION

Two different types of probes are available: end-fire and side-fire probe configurations and transmit frequencies of 6 to 10 MHz (**Figs. 1** and **2**). End-fire probes execute the biopsy in a more

Box 3
Strategies to reduce infectious complications associated with PB

Addition of single-dose aminoglycoside
Rectal swab and targeted antibiotic coverage

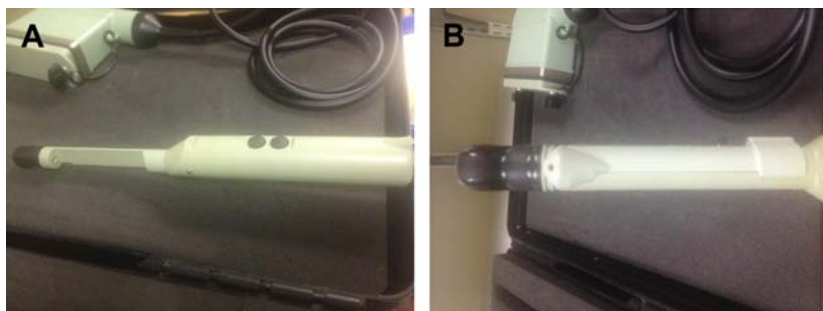


Fig. 1. (A) Side-fire transrectal ultrasound probe. (B) Side-fire transrectal ultrasound probe with needle guide attached.

anteroposterior plane and might therefore allow better access to the most lateral part of the peripheral zone. In addition, targeting the anterior horn of the prostate might be simplified. Evidence from retrospective studies suggests that an end-fire configuration results in greater detection of PCa.^{36,37} However, in a recent prospective randomized multicenter trial,³⁸ no difference was seen in PCa detection rates when a systematic biopsy scheme was adopted. In another study, the side-fire probe was associated with a better patient tolerance profile, which may be related to the size of the tip and the fact that the insertion procedure for the side-fire probe seems to be gentler and better tolerated.³⁹ With these considerations, the choice of probe remains operator dependent. The acoustic properties of soft tissue are similar to those of water, but clinically useful ultrasound energy does not propagate through air. For this reason, a water-density substance, termed a coupling medium, is used. The coupling medium, usually sonographic jelly or lubricant, is placed between the probe and the rectal surface. If the probe is covered with a protective condom, the coupling medium is placed between the probe and the condom, as well as between the condom and the rectal surface. TRUS should be performed in both transverse and sagittal planes.

ANESTHESIA AND PATIENT POSITIONING

Patients are usually placed in the left-lateral decubitus position, with the hips flexed up to 90°. A pillow placed between the knees helps maintain positioning. Make certain that the buttocks are flush with the end of the table to allow manipulation of the probe and biopsy gun without obstruction. Alternatively, some use the dorsal lithotomy position. A repeat DRE should be performed before insertion of the TRUS probe and abnormalities documented.

An important topic is pain control during and after biopsy. The overall sensitivity of the PB is probably only 70%. Many patients have to undergo a repeat biopsy, and this is an important part of AS protocols. If the patient experiences significant pain, it is difficult to convince them about the necessity of repeat biopsy. Periprostatic nerve block (PPNB) with 1% lidocaine is considered the standard anesthetic technique.⁴⁰ The most common site of injection is bilaterally at the junction of the base of the prostate and seminal vesicles, because of the results of anatomic studies showing that the neuroanatomic pathway originates from the inferior hypogastric plexus located at the tip of seminal vesicles and passes between the prostate and rectum.⁴¹ Various infiltration sites

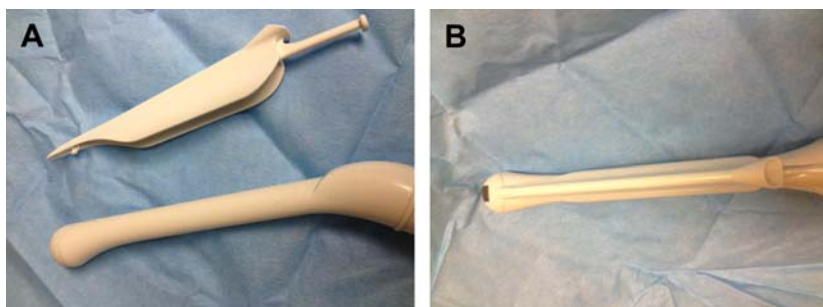


Fig. 2. (A) End-fire transrectal ultrasound probe with needle guide. (B) End-fire transrectal ultrasound probe with needle guide attached.

have been studied (Box 4), including the apex only,^{42,43} bilateral neurovascular bundles,^{44,45} apex and neurovascular regions,^{42,46} 3 locations (base, mid, and apex) posterolateral,⁴⁷ and lateral to the tip of seminal vesicles.⁴⁸ Ismail and colleagues⁴⁹ reported that combined bilateral neurovascular bundles with apical infiltration resulted in more effective reduction in pain associated with TRUS biopsy than bilateral neurovascular infiltration alone, especially in younger patients. However, PPNB does not address somatic pain related to probe insertion and movement, which can be more painful than the biopsy, or pain caused by the infiltration itself. Cormio and colleagues⁴⁶ recently reported their results on using 3 noninfiltrative anesthesia (NIA) protocols for TRUS biopsy. These investigators found that lidocaine-prilocaine cream was most effective in probe-related pain, whereas lidocaine-ketorolac gel was most effective in sampling-related pain. Some investigators have discussed the issue of whether PPNB should be associated with NIA or oral medications.^{50,51} Obek and colleagues⁵⁰ have shown that the combination of PPNB with NIA was superior to PPNB alone. Pendleton and colleagues⁵¹ reported that oral administration of 75 mg tramadol/650 mg acetaminophen 3 hours before PNB seems to provide more effective pain control than PNB alone, without causing any additional side effects.

GRAYSCALE EXAMINATION

Grayscale TRUS is the classic technique for prostate imaging and enables a detailed visualization of the prostate (Fig. 3). Prostate volume should be calculated and PSAD obtained in all patients undergoing TRUS. Volume is determined using the prolate ellipse formula ($\text{height} \times \text{length} \times \text{width} \times 1.83$), which is intrinsic to most modern ultrasonography units. As a general reference, the average prostate volume in a 60-year-old to 70-year-old is approximately 48 mL.

The debate over targeting hypoechoic lesions in the prostate is still unsettled. A biopsy study of

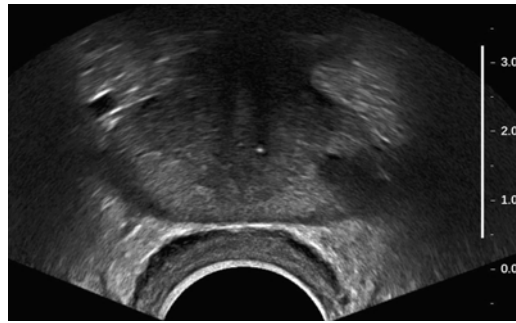


Fig. 3. Grayscale examination of prostate with classically described hypoechoic lesion at left base. Lesion was biopsy proven Gleason 8 (4 + 4) adenocarcinoma of the prostate.

3912 patients published in 2004⁵² revealed that PCa was detected in 25.5% with a hypoechoic lesion and in 25.4% without such a lesion. Even more interesting is the per core distinction, which was 9.3% for hypoechoic and 10.4% for isoechoic areas. On the other hand, Toi and colleagues⁵³ found that biopsies taken when a prostate lesion is identified by TRUS are almost twice as likely to show cancer than when no lesion is visible. The cancers were found to be of higher volume and grade. The investigators concluded that the search for and targeting hypoechoic lesion on TRUS remains important for PCa diagnosis.

BIOPSY TECHNIQUE

The standard device used is a spring-driven 18-gauge needle core biopsy device or biopsy gun, which is passed through the needle guide attached to the ultrasound probe (Fig. 4). The best visualization of the biopsy needle path is often in the sagittal plane. Grayscale images are superimposed with a ruled puncture path that corresponds to the needle guide of the TRUS unit. By



Fig. 4. Example of a spring-loaded automatic 18-gauge PB needle.

Box 4 Sites of injection of PPNB

Bilateral neurovascular bundles
Apex only
Apex and neurovascular bundles
Three locations: base, mid, and apex posterolateral
Lateral to tip of seminal vesicles

design, the spring-loaded biopsy gun advances the needle 0.5 cm and samples the subsequent 1.5 cm of tissue, with the tip extending 0.5 cm beyond the area sampled. Place the tip of the needle approximately 0.5 cm posterior to the prostate capsule before activation. If the needle is advanced through the capsule before firing, this may result in sampling more anterior tissue. As a consequence, the most common site of cancer may be missed. Using the probe to compress the rectal mucosa before firing the needle may reduce rectal bleeding. The biopsy sample is placed in formalin solution provided by the reference laboratory. Sample submission can vary and is discussed later.

NUMBER AND SITE OF BIOPSY CORES

A laterally directed systematic TRUS-guided PB with 12 cores is considered the standard procedure for PCa detection, resulting in a positive biopsy rate of 25% to 50%.^{6,54,55} Fig. 5 shows the recommended biopsy location and direction of a typical TRUS 12-core biopsy template.

Several studies have reported the higher yield of an EPB versus the old standard sextant biopsy, without an increase in the detection of insignificant cancer.^{55,56} The debate continues as to whether there is a value in adjusting the number of cores based on age or prostate volume.⁵⁷⁻⁵⁹ Sampling

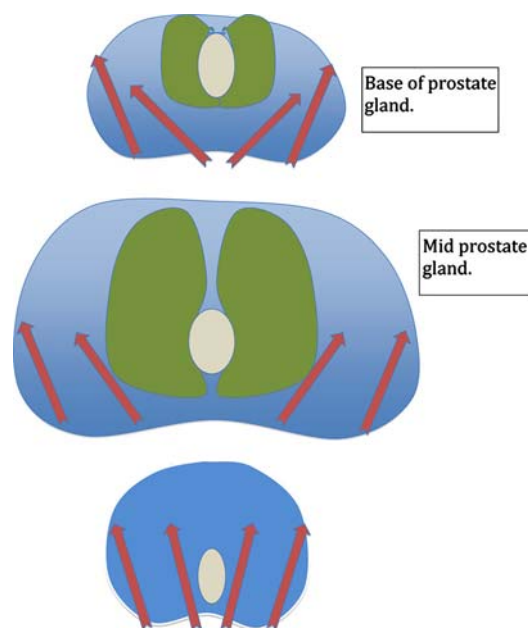


Fig. 5. Recommended systematic 12-core PB at base, mid, and apical prostate gland. Blue represents peripheral zone, the focus of the biopsy needle. Green represents the transition zone and tan represents the urethra.

accuracy tends to decrease progressively with an increasing prostate volume. Ploussard and colleagues⁶⁰ proposed that an extended biopsy scheme, with 21 cores obtained, increases cancer detection rates, especially if PSAD is less than 0.20 ng/mL.

On the other hand, it has been shown that the saturation technique as an initial PB strategy does not improve cancer detection. Jones⁶¹ has suggested that further efforts at extended biopsy strategies beyond 10 to 12 cores are not appropriate as initial biopsy strategy. In a systemic review, Eichler and colleagues⁶² showed that there is no significant benefit in taking more than 12 cores and methods requiring more than 18 cores have a poor side-effect profile. The AUA consensus has suggested that a 12-core biopsy is the recommended initial biopsy scheme; other investigators have advocated for additional biopsies, such as the 14-core biopsy by Mousa and colleagues.⁶³

In addition to the number of cores and prostate volume, the concept of biopsy core direction is equally important. The apex and the base of the peripheral gland are the most common cancer sites, which is where biopsies should be directed, whereas the parasagittal biopsies have been shown to have the lowest possibility of PCa at the initial biopsy.^{57,64-66} Based on landmark anatomic PCa location studies⁶⁷ and furthered by knowledge of tumor location by Stamey,³ the addition of laterally directed biopsies has been shown to yield an approximately 5% to 35% increase in cancer detection rates.^{56,64} Most of the extradetected cancers were in anterior apical and far lateral midlobar regions, 2 areas well sampled by EPB. Contrary to earlier findings regarding the importance of parasagittally directed cores to detect transitional zone (TZ) cancer,⁶⁷ it now seems established that because of their low prevalence at initial biopsy, cores of this area should be abandoned.⁵⁴ Researchers from the University of Washington reported their experience with obtaining biopsies from the anterior apical region.⁶⁶ These biopsies were directed under the capsule with the goal of sampling the peripheral zone anterior and distal to the TZ at apex. These investigators reported that the most common unique site of cancer was the anterior apex, where 17% of cancers would have been missed if not sampled. The use of EPB has resulted in more Gleason score concordance. San Francisco and colleagues⁶⁸ reported an improvement on concordance rate from 63% to 72%. Milan and colleagues⁶⁹ reported that rate of upgrading to worsening cancer was significantly reduced with EPB. With EPB, the risk of significant upgrading

decreases because of higher sampling density and more accurate pathologic biopsy evaluation. The AUA has recently completed a white paper confirming that a 12-core systematic biopsy is optimal and that there was not compelling evidence that individual site-specific labeling of cores benefits clinical decision making regarding the initial management of PCa. The investigators recommend packaging no more than 2 cores in each jar to avoid reduction of cancer detection rates through inadequate tissue sampling.⁷⁰

QUALITY ASSURANCE

Benign or malignant conditions of the prostate are diagnosed by nuclear and architectural examination of prostate tissue. Therefore, 2 important factors are important in assessing the adequacy of a biopsy, namely, core length and the presence of glandular elements (Box 5). Boccon-Gibod and colleagues⁷¹ suggested that the average needle biopsy length should serve as a measure of quality control, with 10 mm of tissue as the shortest acceptable length. Iczkowski and colleagues⁷² noted that the length of a single core sampled by sextant biopsy varied more than 3.6-fold. These investigators reported that a longer total tissue length increased the cancer detection rate, but this finding attained statistical significance only for cores obtained at apex. Obek and colleagues⁷³ showed that a significant correlation with needle core length and cancer detection rates exists for all biopsy cores and is not limited to a specific prostate site. These investigators established a cutoff to predict a higher cancer detection rate and, thus, a potential core quality assessment tool. Obtaining cores longer than 11.9 mm was associated with 2.5 times higher likelihood of detection of PCa. Core length may vary according to different factors, including but not limited to the urologist who performs the biopsy, the needle, the biopsy retrieval and tissue handling methods, and the pathologic analysis.^{71,72} To investigate the adequacy of the samples obtained by PBs, Dogan and colleagues⁷⁴ evaluated cores obtained from 378 patients. These investigators found that the highest incidence of absence of glandular elements was detected at apical and far lateral biopsy samples. Absence of glandular elements in 1, 2,

and 5 biopsy samples were 50%, 27.8%, and 16.1%, respectively. The results have been found to be operator dependent. For patients with PSA between 4 and 10 ng/mL, cancer detection rates was lower in patients with absence of glandular elements. Collectively, these data suggest that clinicians must evaluate the pathology report in detail regarding core length and the presence of glandular elements. Pathologists must inform clinicians if they notice inadequacy of samples, and clinicians should even repeat the biopsy in necessary cases.

REPEAT PB AFTER INITIAL NEGATIVE BIOPSY

Studies of repeat PB after negative EPB indicate that up to 30% of patients have cancers that were not previously identified.^{75,76} Repeat PB seems to be justified in men with an initial negative biopsy but persistent suspicion of PCa based on age, comorbidities, DRE findings, repeated PSA measurements, other PSA derivatives (% free PSA, complexed PSA, PSAD, PSA velocity), or urinary PCA3 score.⁶ The use of the ProgenSA PCA3 assay (Hologic Gen-Probe, San Diego, CA, USA), which uses a PCA3 score with a cutoff value of 25 in post-DRE first-catch urine, has been approved by the US Food and Drug Administration to aid in the decision for repeat PB in men with 1 or more previous negative biopsies.⁷⁷ The cutoff value remains debatable, because some studies have used 35 as the cutoff of abnormal.^{78,79} The superiority of PCA3 score compared with % free PSA was shown, indicating that a lower PCA3 score may prevent unnecessary repeat PB.^{80,81} PCA3 seems to have a role in reducing unnecessary PB at first repeat PB but not at second or more repeat PB sessions.⁸²

The number of biopsies needed in the repeat settings is still debatable. The NCCN guidelines suggest performing a second extended protocol and considering saturation biopsies only in patients with high risk of cancer after multiple negative biopsies.⁶ Several studies support the hypothesis that saturation biopsy (>20 cores) seems appropriate in the repeat biopsy setting.^{76,83,84} In a study from Italy,⁸⁴ the best re-biopsy scheme varied according to the clinical characteristics of the patients. For patients with no atypical small acinar proliferation (ASAP), the ideal number of cores varied according to % free PSA. If % free PSA was less than 10%, the best scheme was a 14-core biopsy (including 4 TZ biopsies), whereas if % free PSA was greater than 10%, then the ideal scheme would include 20 core biopsy (including 4 TZ biopsies). In addition to the number of biopsies, location is an important issue in repeat biopsy. According to

Box 5

Factors important in assessing adequacy of PB

Core length

Presence of glandular elements

the European Association of Urology (EAU) 2013 guidelines, TZ biopsies should be considered in the repeat setting.⁸⁵ In addition, the anterior apex seems to be the most common site of single-focus PCa, and repeat biopsies should include this distinct location.^{76,86,87} Djavan and colleagues⁸⁸ reported in 2001 an original work on the risk of PCa on repeat biopsies performed 6 weeks after an initial negative set. These investigators found that cancer detection rates on biopsies 1, 2, 3, and 4 were 22%, 10%, 5%, and 4%, respectively, and that 58%, 60.9%, 86.3%, and 100% of patients who had RP had organ-confined disease on biopsies 1, 2, 3, and 4. The investigators concluded that biopsy 2 in all cases of a negative finding on biopsy 1 seems justified; however, further biopsies should be obtained only in select patients. Two important points need to be stressed: there was minimal delay between biopsies and these biopsies were all sextant. Thus, these findings may not apply in the modern extended biopsy era. Campos-Fernandes and colleagues⁷⁵ in a more recent cohort with extended biopsies found that 18%, 17%, and 14% of patients had PCa in second, third, and fourth biopsies, respectively. Cancer detected at these sets of biopsies was significant in 85% of cases. Similarly, Tan and colleagues⁸⁹ found significant PCa detected on third or greater PB, underscoring the importance of repeat biopsy in the setting of increased or increasing PSA despite negative previous PB. Pelvic magnetic resonance imaging (MRI) may be used to further investigate the possibility of an anterior located PCa in selected patients. Thus, no definitive recommendation can be made on when to stop biopsies when there is concern, and the decision should be individualized.

Another issue in the repeat biopsy setting is the role of transurethral resection of the prostate (TURP). Several investigators have reported the PCa detection rate offered by TURP.^{90,91} However, the 2013 EAU guidelines⁹² state "the use of diagnostic TURP instead of repeat biopsies is a poor tool for cancer detection." The NCCN 2012 guidelines⁶ recommend TZ biopsies as part of repeat biopsy strategy, but they do not specifically comment on TURP. In a recent European study,⁹³ in which patients were randomized to saturation biopsy only or saturation biopsy 1 TURP, TURP increased the detection of clinically significant cancer. The investigators comment that this strategy has to be balanced against the small increased incidence of urinary retention, emergency readmission, and longer hospital stay.

The role of transperineal biopsy in the repeat setting is debatable. The theoretic advantage of

the transperineal route over the transrectal route stems from the direct longitudinal access to the prostate gland, potentially resulting in more efficacious sampling of the peripheral apical region, which seems to be underrepresented in the transrectal route. Several researchers have shown encouraging results with the use of template transperineal biopsies.^{94,95} However, this strategy has to be weighed against the need for anesthesia and increased morbidity with such an invasive procedure. Modern imaging studies such as MRI might have a relevant role in visualizing clinically significant cancers to facilitate precise sampling from any suspicious areas.

REPEAT PB AFTER SUSPICIOUS OR POSITIVE INITIAL BIOPSY

Suspicious pathologic findings, including ASAP and high-grade prostatic intraepithelial neoplasia (HGPIN) in previous biopsy may be an indication for repeat PB. ASAP describes a situation in which the pathologist is unable to establish the diagnosis of PCa. The incidence of ASAP ranges between 0.7% and 23.4%, with a median incidence of 4.4%.^{87,96} It is an almost certain clinical indication for a rebiopsy, because approximately 40% of patients are found to have cancer, even in the extended biopsy era.^{8,97,98} Allen and colleagues⁹⁹ reported that the chance of detecting cancer is greatly increased by performing a rebiopsy not only of the atypical site but also of the adjacent contralateral and adjacent ipsilateral areas. In general, a biopsy is performed within 3 to 6 months. Scattoni and colleagues⁸⁴ suggest obtaining 14 cores with no TZ biopsies in patients with previous diagnosis of ASAP.

HGPIN at PB is found in between 0% and 24.6% of patients, with a median incidence of 4.7%.⁸⁷ It represents a discrete pathologic entity and is a potential precursor lesion to PCa.¹⁰⁰ A single focus of HGPIN does not warrant a repeat biopsy, but controversy persists about whether the presence of multifocal HGPIN truly represents an important risk factor for consideration of a repeat biopsy. Initial reports, based on sextant biopsies, showing a high prevalence of cancers in rebiopsies have not been reproduced in the extended biopsy era.⁸⁷ Based on level 2a evidence, the EAU⁸⁵ does not recommend repeat biopsy in the presence of HGPIN. However, some investigators suggest that multifocal HGPIN carries a 40% risk of cancer in subsequent biopsies and recommend a repeat biopsy within 1 year.^{101,102} Godoy and colleagues¹⁰³ have reported a continued risk of PCa development in these patients, regardless of

changes in PSA, and proposed a delayed-interval biopsy every 3 years.

Repeat biopsy at 3 to 18 months from diagnosis of low-risk PCa, in patients who opt for AS, has been suggested to reduce misclassification.^{104,105} Several investigators¹⁰⁶ found that approximately 1 in 3 patients considered candidates for AS have more significant disease. In addition, in AS protocols, surveillance biopsies, to determine progression, are performed at intervals of every year to every 3 to 4 years.¹⁰⁶ The optimal number and location of biopsies in AS protocols has not been established. The use of other parameters such as PCA3 score and MRI in selecting patients for AS protocols is under study.^{107,108}

IMAGE-GUIDED ENHANCEMENTS FOR PB

PB through a center of cancer contains more tissue, which allows more accurate characterization for pathologic interpretation. Thus, modalities that allow for visualization of PCa may aid in image-guided PB. Several technologies are being evaluated, namely color Doppler ultrasonography, MRI, and elastography.¹⁰⁹ An important and obvious limitation of the image-guided PB techniques is that they are operator dependent and require significant radiologic expertise and cooperation with radiologic experts.

COLOR DOPPLER ULTRASONOGRAPHY

PCa is associated with angiogenesis and neovascularization; this is also seen by increase in microvessel density (Fig. 6).¹¹⁰ It is estimated that as a

result of these factors, a disturbed perfusion of malignant tissue compared with normal prostate tissue is present.^{111,112} Contrast-enhanced ultrasound (CEUS) imaging was developed to image perfusion.^{113,114} Ultrasound contrast agents consist of small encapsulated gas bubbles that can be administered intravenously and remain intravascular. Adding microbubbles as additional reflectors into the blood stream increases the sensitivity of color Doppler and power Doppler imaging. However, these techniques use relatively high ultrasound energy levels and, as a result, a large proportion of the microbubbles are destroyed as they are imaged.¹¹⁵ During the last few years, new imaging techniques have been developed that enable sensitive microbubble imaging even in microvasculature, with lower destruction rates (low mechanical index imaging). A long list of CEUS techniques is available, from harmonic imaging, using the nonlinear behavior of microbubbles in an ultrasound beam, via pulse inversion techniques, using various pulses to isolate the nonlinear reflections, to even more specific imaging techniques that provide selective imaging of the signal reflected by the bubbles, canceling most of the tissue reflections.¹¹⁶ CEUS imaging has been extensively studied, with 2 main objectives, namely, to increase the diagnostic yield of the biopsy and in addition to detect more clinically significant cancers.

Two studies reported on the value of CEUS and found that targeted biopsies detected as many cancers as systemic biopsies, with fewer than half the number of biopsy cores.^{117,118} Linden

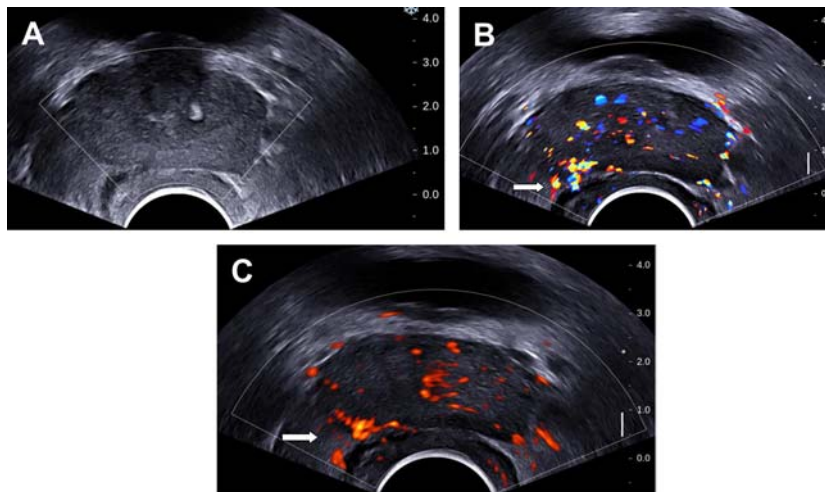


Fig. 6. (A) Routine grayscale examination of prostate with no suspicious lesions seen. (B) Color Doppler examination; increased vascularity noted in right base; which proved to be a Gleason 7 (3+4) cancer (arrow). (C) Power Doppler image showing the Gleason 7 cancer at right base (arrow).

and colleagues¹¹⁹ used CEUS to compare it with systemic biopsy in 60 patients and concluded that the vascularity detail allowed directed biopsy of these areas, with increased detection of PCa. Nelson and colleagues¹²⁰ showed a sensitivity of 29% and a specificity of 80% for the CEUS-targeted biopsies. Halpern and colleagues¹²¹ concluded that CEUS improves the sensitivity of PCa detection without substantial loss of specificity. In a recent Chinese study, the sensitivity and negative predictive value of CEUS-targeted biopsies was significantly better than standard biopsy.¹²² However, in all studies, CEUS techniques alone would miss many tumors, and researchers suggest targeted biopsies to areas of abnormal flow in addition to systemic biopsies.

Mitterberger and colleagues¹¹⁷ found that the Gleason score detected by CEUS was higher than that detected by standard biopsy. In a study of 690 men, the mean Gleason score was 6.8 for CEUS versus 5.4 for standard biopsy. Jiang and colleagues¹²³ correlated findings between CEUS techniques, Gleason score, and microvessel density and found similar results. Halpern and colleagues¹²⁴ reported excellent accuracy of CEUS for the detection of high-grade cancer, with greater than 50% biopsy core involvement. This finding may have profound implications in detecting higher-grade cancers and might be particularly useful in patients who opt for AS.

Morelli and colleagues¹²⁵ evaluated the ability of a phosphodiesterase type 5 inhibitor vardenafil to increase prostate microcirculation visibility. Analysis of standard technique, contrast, and vardenafil-enhanced CEUS findings by biopsy core showed significantly higher detection rates using vardenafil versus contrast and standard techniques (41.2% vs 22.7% and 8.1%, respectively). Methods to decrease the blood flow related to benign causes and thereby increase the sensitivity of blood flow-directed biopsy techniques have been performed. In a randomized, double-blind, placebo-controlled study, Halpern and colleagues¹²⁴ found that pretreatment with dutasteride had no significant impact on the detection of PCa.

MRI

MRI has been shown to have a high degree of accuracy in the detection of clinically significant cancer when compared with RP specimens.¹²⁶ When functional parameters, such as dynamic-contrast enhancement, diffusion-weighted imaging, and spectroscopy are used, in addition to standard T1-weighted and T2-weighted sequences, MRI may afford an opportunity for image-guided approach to the prostate.¹²⁷ A recent systemic

review of MRI-derived targets¹²⁸ reported that cancer was detected in 30% of targeted cores versus 7% of systematic cores. MRI lesions can be targeted either within the magnet or by allowing a lesion defined on MRI to be identified on ultrasound during a TRUS-guided procedure. MRI-guided biopsies within the magnet are difficult to perform because of high costs, long intervention time, and poor ergonomics.^{129,130} MRI during a TRUS-guided PB setting can be used either visually or with computerized MRI-TRUS image registration.^{131,132} Delonchamps and colleagues¹³³ found that PB combined with MRI-TRUS image registration improved significantly cancer detection over systemic or visually aided PB. Similarly, Pinto and colleagues¹³⁴ showed that MRI detected more cancer per core than a standard 12-core biopsy.

ELASTOGRAPHY

Elastography is an ultrasound imaging technique based on the concept that significant differences exist between elastic properties of benign and malignant tissue (Fig. 7).¹³⁵ It is able to detect the change in reflection of sound waves when manual compression is applied to the tissue. Current studies suggest that using a real-time elastography (RTE) targeted approach, using less than half of the biopsy cores in the EPB approach, results in an equivalent PCa detection rate.^{135,136} Nelson and colleagues¹²⁰ compared systematic PB and

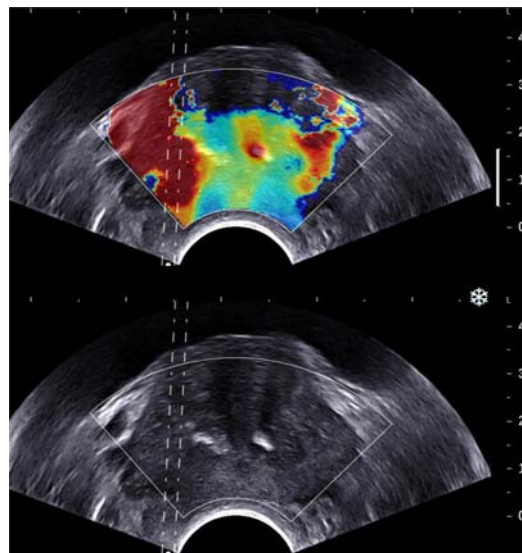


Fig. 7. Gleason 6 cancer right midprostate visualized on elastography (top panel) and not detected on routine grayscale imaging. Dotted lines represent projected path of biopsy needle.

targeted biopsies with grayscale, color Doppler, and RTE. Targeted biopsies based on elastography were twice as likely to yield a cancer diagnosis, with a trend toward higher-grade cancers. No abnormality on elastography or other sonographic modality was seen in 53.8% of positive systematic biopsy cores. Brock and colleagues¹³⁷ prospectively randomized 353 patients to either undergo RTE and grayscale TRUS. Both groups were comparable in terms of age, PSA, prostate volume, and clinical stage. RTE guidance showed an 11.7% higher detection rate of PCa. Sensitivity for visualizing PCa using RTE was 60.8% compared with 15% using gray scale. Thus, the sensitivity remains low, and a systematic biopsy approach remains mandatory. Shear-wave elastography is an alternative system using acoustic radiation force impulse to generate a shear wave. It has the advantage of being less operator-dependent, because it does not require manual application of pressure and the results are normally presented in absolute numbers. Two small studies were reported, with encouraging results, and the use of this technique continues to evolve.^{124,138}

COMPLICATIONS OF PB

Urologic side effects of the procedure (Table 2) include UTI, bleeding (hematuria, bleeding per rectum, or hematospermia) and acute urinary tract obstruction. The increased number of biopsy cores, rates of bacterial resistance,²⁷ an increase in the use of antiplatelet agents,¹³⁹ and a high prevalence of benign prostatic hyperplasia (BPH)¹⁴⁰ have all contributed to increased morbidity associated with TRUS biopsy. Complications associated with PB had a prominent role in the US Preventative Services Task Force 2012 recommendations against PCa screening.¹⁴¹

Table 2
Summary of common complications reported from transrectal PB

Complications	%
Hematospermia	37.4
Hematuria >1 d	14.5
Rectal bleeding <2 d	2.2
Prostatitis	1.0
Fever >101.3°F, epididymitis, rectal bleeding >2 d, retention	<1.0
Other complications requiring hospitalization	0.3

Data from EAU Guidelines. Available at: <http://www.uroweb.org>. Accessed February 21, 2012.

In a large population-based study from Ontario, the probability of being admitted to hospital within 30 days of the procedure increased 4-fold between 1996 and 2005.²⁵ The overall 30-day mortality was 0.09% and did not change over the study period. When analyzed by cancer status, the 30-day admission rate was 1.9% for patients without cancer versus 0.8% for patients with cancer. The mean time to hospital admission from TRUS biopsy was 5 days. Most hospital admissions were for infection-related complications (71.6%), followed by bleeding-related diagnosis (19.4%) and urinary obstruction-related diagnoses (9.0%). The rates of hospital admissions related to infection increased from 0.6% in 1996 to 3.6% in 2005. This increase is probably related to a multitude of factors, including lack of standardization of antibiotic prophylaxis protocol, use of mechanical bowel preparation, and the emergence of fluoroquinolone-resistant organisms.

The hospital admission rates for patients undergoing repeat biopsy, when normally more cores are obtained, were not higher than those undergoing a first biopsy. Also, studies that compare the sextant pattern and the extended pattern of biopsies showed no significant increase in morbidity.^{142,143} There was a small increase in complications related to urinary tract obstruction, which may have resulted from higher prevalence of BPH in an aging population.¹⁴⁰ A steady rate of bleeding-related complications is consistent with findings that men taking low-dose aspirin did not have increased rates of bleeding.¹³⁹ The same researchers found that patients of physicians who performed a high volume of biopsies experienced a low 30-day hospital admission rate.

SUMMARY

Grayscale TRUS PB using local anesthesia remains the standard approach to the definitive diagnosis of PCa. Careful patient evaluation and preparation are essential to maximize the results and minimize the complications of the biopsy procedure.

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Office-based Management of Nonmuscle Invasive Bladder Cancer

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KEYWORDS

• Bladder cancer • Office-based management • Surveillance • Recurrence • Fulguration

KEY POINTS

- Office-based management of the bladder can be used in low risk-stratified patients to reduce costs and burden of care.
- Smoking cessation and narrow-band imaging may play important underevaluated roles in the future management of bladder cancer.

INTRODUCTION

Bladder cancer is the fifth most common malignancy in the United States, but it is estimated to be the most expensive lifetime cancer due to the high cost of surveillance. In select patients with a history of low-grade and noninvasive tumors, office-based surveillance may be oncologically safe, with significant reductions in cost and complications from operating room transurethral resection (TUR). This article attempts to identify the ideal candidates, as well as management and surveillance strategies of low-grade bladder tumors in the office-based setting.

NATURAL HISTORY OF NONINVASIVE BLADDER CANCER

Over 2.7 million people live with bladder cancer,¹ and over 380,000 incident bladder tumors were identified annually worldwide in 2008,² including 73,000 tumors in the United States.³ In fact, bladder cancer is the fifth most common cancer in the United States. The worldwide age-

standardized rate (ASR) for bladder cancer is 10.1 cases per 100,000 men and 2.5 cases per 100,000 women, with a mortality rate of 4 deaths per 100,000 men and 1.1 deaths per 100,000 women.⁴ Most bladder tumors identified are nonmuscle invasive (75%–85%). Of nonmuscle invasive bladder tumors, 70% are stage pTa; 20% are stage pT1, and 10% are carcinoma in situ (CIS).⁵ The overall rate of recurrence for nonmuscle invasive bladder cancer is 48%,⁶ with a range of 31% to 78% at 5 years, ranging from low to high risk.^{6,7} In a prospective study of 215 patients from Memorial Sloan-Kettering Cancer Center (MSKCC), low-grade bladder tumors were found to have a recurrence rate of 31% (papilloma), 52% (papillary urothelial neoplasm of low malignant potential [PUNLMP]), and 72% (TaLG), with a median time of recurrence of 72 months for PUNLMP and 18 months for TaLG.⁸ Progression occurred in 8% of TaLG patients, with those progressing more likely to have multiple tumors, more frequent recurrences, and require more operative TUR procedures. Progression by grade occurred in 3% of cases, and progression by

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stage (T1) occurred in 5% of cases. Progression was heralded by conversion from negative to positive cytology in 71% of cases (12/17).⁸ Risk factors for progression include >1 tumor (2-fold increase),⁹ recurrence at 3-month cystoscopy,^{8,10,11} prior recurrence rate of >1 recurrence per year,¹² and size of tumor >3 cm.^{13,14} No patients with PUNLMP or papillomas progressed.⁸ Thus, low-grade bladder cancer has a low risk of progression despite a high rate of recurrence.

COST OF MANAGEMENT OF LOW-GRADE BLADDER CANCER

Depending on the model and breadth of features included, bladder cancer has been estimated as the most expensive cancer to health care systems, with a mean cost to Medicare of \$96,000 to \$187,000 per patient in 2001.¹⁵ In the United States, the total estimated cost in 2006 was \$206 billion, with predicted productivity loss of \$17.9 billion, and cancer-related morbidity of \$110 billion.¹⁶ The majority of the cost for bladder cancer is hospital-based transurethral resection of a bladder tumor (TURBT), estimated to be responsible for 71% of the cost of bladder cancer in the United Kingdom.¹⁷ In a single-institution study, the mean cost per patient with bladder cancer from a period of 1991 to 1999 was \$65,158 measured at MD Anderson. The main expense per patient was due to admission (\$16,778, 26%) and surgical procedures (\$15,781, 24%), with the remaining costs due to surveillance.¹⁸ These prices could be dramatically reduced if patients were managed in the office setting. In a comparison of outpatient TUR (estimated to cost between \$2666 and \$2113), office fulguration was estimated at only \$1167. Routine use of office-based fulguration could mitigate the role of single-dose intravesical therapy after TURBT. Single instillation of postoperative chemotherapy decreases recurrence rates by up to 13%, with possible complications including chemical cystitis. Using Markov state transitional modeling, the cost of office-based fulguration was compared with inpatient TURBT.¹⁹ The cost for outpatient fulguration without perioperative chemotherapy was \$1115.21, compared with \$3436.34 for inpatient TUR. Using sensitivity analysis, the authors found that with a recurrence rate of >14%, the use of repeated office fulgurations was more cost-effective than perioperative intravesical chemotherapy instillation.

IDENTIFICATION OF PATIENTS FOR OFFICE-BASED MANAGEMENT OF BLADDER CANCER

The critical factor to determine the suitability of office-based management of bladder cancer is

an accurate assessment of risk of progression. Although the initial identification of bladder cancer occurs in the office, the authors recommend outpatient TUR with examination under anesthesia for complete and accurate staging. Based on TUR pathology, tumors amenable to office-based management are papillomas, PUNLMP, and TaLG tumors. The main concern with office-based management is missing progression to higher stage or grade, which would warrant greater resection and/or intravesical therapy. No prospective trials have determined the best candidates for office-based fulguration. Donat and colleagues²⁰ described successful management of low-grade tumors with no recurrence within 6 months of their initial TUR. All tumors were smaller than 0.5 cm, with a negative urine cytology. The risk of progression in this group is approximately 8%.⁸ Using data from 2596 patients from 7 European Organisation for Research and Treatment of Cancer (EORTC) trials, risk for individual patients can be calculated. The Donat criteria would suggest a yearly progression risk of 1%, and by 5 years, a progression of 6% (intermediate risk of progression based on <http://www.eortc.be/tools/bladdercalculator/>).⁶ Thus, patients with a risk score of 6 or less would be potential candidates for office-based management.

One of the most important elements of office-based management is the accurate visual diagnosis of papillary or low-stage and -grade tumors. Urologists were able to predict low-grade and -stage tumors using flexible cystoscopy in 93% of cases with 99% accuracy if cytology was included in a study of 144 tumors.²¹ In a larger study of over 500 patients, only 5% of tumors were inaccurately categorized as noninvasive by flexible cystoscopy.²² Yet, series from other institutions suggest that urologists have a lower accuracy to predict grade, with only 26 of 49 (53%) predicted accurately by cystoscopy.²³ Thus, the correct determination of risk by nomograms and visual observation plays a pivotal role in choosing patients for office-based fulguration. The experience of the urologist is a critical factor for successful outpatient management of low-grade papillary bladder tumors.

EFFECTIVENESS AND TOLERABILITY OF OFFICE-BASED MANAGEMENT

Herr described the use of office-based cystoscopy with fulguration in 69 patients with both high- and low-grade lesions, some of which demonstrated invasion.²⁴ Of the 32% of patients who required TUR, 5 had CIS, and 3 had muscle invasion. Office-based fulguration was the only intervention in 68% of

patients, with 30% of patients requiring repeat treatment. In a prospective study of 267 patients carefully selected (as per the Donat criteria), office-based fulguration was the only intervention required in 60% of patients,²⁰ with a median follow-up of 6.8 years and 2.2% dying of bladder cancer. Patients who underwent TUR (higher risk) had no difference in progression compared with cystodiathermy, suggesting appropriate risk-based management. In a series of 91 patients treated with office-based fulguration with local anesthetic, 12% found it painful, but 90% of procedures were completed within 5 minutes, with none lasting longer than 10 minutes.²⁵ At 15 weeks, 59% of patients had no recurrence, and only 6% of patients had recurrence at the site of treatment. Wedderburn and colleagues²⁶ described 103 patients managed with cystodiathermy, with an overall recurrence rate of 49% and 12% recurring at or near the site of treatment. When rated for discomfort, an average visual analog pain scale of mild or negligible was reported by 80% of patients. These data suggest that in carefully selected patients, office-based cystodiathermy can be performed safely and comfortably with reasonable recurrence outcomes.

WATCHFUL WAITING OF IDENTIFIED BLADDER TUMORS

Some patients with small or low-grade bladder tumors may be watched without the need for TUR or cystodiathermy after identification of new tumors. Soloway and colleagues²⁷ described observation of 32 patients with a mean duration of 10.8 months, and patients undergoing an average of 1.8 interval cystoscopies between treatments (range of 1–5). Importantly, the authors described a tumor growth rate of 1.77 mm per month, with a progression rate of 6.7%. Gofrit and colleagues²⁸ described the active surveillance of 38 tumors in 28 patients, with surveillance halted for tumor size (9 patients), increased number (19 patients), or hematuria. All tumors were Ta on TUR. The authors noted that if the initial tumor was smaller than 5 mm, the growth rate was significantly less than if the tumor was >5 mm. Pruthi and colleagues²⁹ described the expectant management of 22 patients with low-grade bladder tumors. Over 25 months, 8 patients had no growth of identified tumors; 9 patients had minimal growth, and 5 patients had moderate growth. Sixty-eight percent of patients required no intervention; 14% required office cystodiathermy, and 18% required TUR. Only 9% of patients had progression, half (1 patient) of whom had stage progression. Thus, watchful waiting may be a strategy to consider in patients with significant

comorbidities, on blood thinning agents, and having small tumors of <0.5 cm.

FREQUENCY AND TIMING OF FOLLOW-UP AND TUMOR SURVEILLANCE

No prospective randomized trials have demonstrated sufficient level of evidence to support a specific surveillance protocol for the management of noninvasive bladder tumors. The goals of surveillance would be to minimize the cost and psychological burden of surveillance, tempered by prudent follow-up to prevent growth of tumors necessitating inpatient TUR. From watchful waiting studies, it has been noted that small tumors (<5 mm) may be observed for almost 10 months without intervention.²⁸ Yet, to prevent an operative TUR, one could argue that repeated cystodiathermy may be prudent at decreased intervals. Thus, cystoscopic tumor surveillance (from the National Comprehensive Cancer Network [NCCN] 2013) is recommended at 3 months and then subsequently at increasing intervals.³⁰ The European Association of Urology (EAU) recommends a cystoscopy at 3 months, then 9 months, then yearly for 5 years for low-risk tumors.⁴ Many urologists manage low-risk tumors similar to higher-risk tumors and perform cystoscopy every 3 months for the first 2 years, every 6 months for 2 years after, and yearly thereafter. Clearly this is an area of future clinical research to determine the appropriate follow-up interval for low-grade tumors to minimize cost and intervention but not increase risk of bulky recurrence.

VOIDED BIOMARKERS FOR SURVEILLANCE

The use of prognostic biomarkers could potentially play a critical role in the management of patients with low-grade bladder cancer. Invasive procedures, such as cystoscopy, could potentially be avoided if a biomarker reliably had a high negative predictive value. There are several biomarkers approved for surveillance by the US Food and Drug Administration. Voided cytology has a long-documented role in the identification of high-grade bladder cancer and can be used to identify patients who require further intervention.³¹ The sensitivity ranges from 13% to 75% (median 35%); specificity ranges from 75% to 95% (median 94%).³² Although a positive cytology is a predictor of high-grade bladder cancer, atypical and suspicious cytologies are more troubling to the urologist without a clear indication for intervention. Limitations of cytology include interobserver variability and artifact associated with fixation. NMP22 is a point-of-care test with a sensitivity

ranging from 47% to 100% (median 54%), and a specificity ranging from 55% to 98% (median 78%).³³ The Urovysn fluorescence in-situ hybridization (FISH) has a sensitivity of 70% to 86% (median 79%) and a specificity ranging from 66% to 93% (median 70%).³⁴ BTastat is a point-of-care marker that can be tested at home by the patient, with a sensitivity of 29% to 74% (median 58%) and specificity of 56% to 86% (median 73%).³⁵ There are currently no markers that reliably outperform cystoscopy for detection of a bladder cancer recurrence, or have been demonstrated to be more accurate in prospective trials.³² In a study of patients undergoing cystoscopic surveillance for bladder cancer, 75% described anxiety related to missing cancer from voided markers and desired a test with 95% sensitivity to identify a bladder recurrence to forgo cystoscopy.³⁶

ROUTINE IMAGING FOR SURVEILLANCE

Progression of low-grade bladder cancer to upper tract or extravesical tumors occurs at a frequency of 40% at 15 years, including upper tract and prostate involvement.³⁷ In low-grade disease, this risk of upper tract progression was 8%, with a median time to development of 29 months.⁸ The EAU recommends no upper tract surveillance for low-risk tumors but yearly surveillance for high-risk bladder cancer.⁴ The rate of upper tract progression increases yearly, and although routine surveillance should increase detection, only 29% of new upper tract tumors were detected by axial imaging in asymptomatic patients,³⁸ with the remainder presenting with symptomatic recurrence.

ANTIBIOTICS, PROPHYLAXIS, AND DRUG RESISTANCE

Asymptomatic bacteria is commonly found in elderly patients, and those instrumented for malignancy may be at an increased risk for symptomatic infection.³⁹ Patients with bladder cancer will undergo many cystoscopies during their lifetime, and unsupervised use of antibiotics to treat colonization rather than infection, even when given for procedural prophylaxis, may result in multidrug bacterial resistance. Routine use of antibiotics is recommended by the American Urological Association (AUA) best practice guideline after cystoscopy performed for bladder cancer surveillance.⁴⁰ This recommendation is based largely on best practice. A retrospective study of patients receiving cystoscopy without antibiotic prophylaxis identified a febrile infection rate of 3.5% in patients with infected urine or 1% in patients having uninfected urine.⁴¹ A randomized trial of antibiotics versus no

antibiotics with flexible cystoscopy was halted early due to a low infection rate in the untreated cohort of 0.85%.⁴² These data suggest that despite a best practice statement, prudent antibiotic stewardship may lead to decreased prophylaxis use in asymptomatic patients undergoing cystoscopy and will reduce costs.

LIFESTYLE MODIFICATION

One of the most important lifestyle changes the urologist can contribute to the overall health of patients and potentially decrease the rates of bladder tumor recurrence is counseling for smoking cessation. Duration and intensity of smoking are directly correlated to bladder cancer recurrence in patients with noninvasive bladder cancer.⁴³ Patients report poor knowledge regarding the association with smoking and their bladder cancer, and most describe increased readiness to quit if they knew their bladder cancer was possibly caused by smoking (5-fold greater wish to quit than controls without cancer).⁴⁴ The urologist may play a more active role in smoking cessation in the future. Urologists who spent 5 minutes involved in smoking cessation had a 4.6-fold increased rate of smoking cessation and a 7.5-fold increased rate if nicotine replacement was utilized.⁴⁵ At 10 years after quitting, smoking cessation decreases the risk of disease recurrence.⁴⁶

Many studies have attempted to determine the utility of supplements to decrease the high rates of bladder cancer recurrence. Despite promising retrospective data on vitamin A, no prospective studies have demonstrated a benefit in decreasing rates of bladder cancer recurrence.⁴⁷ Vitamin E and selenium were not demonstrated to improve prevention of bladder cancer in large population-based trials.⁴⁸ The probiotic *Lactobacillus casei* (LC) decreases mutagen and carcinogen production by flora of the gut from ground beef and may potentially decrease the risk of cancer recurrence.⁴⁹ Habitual ingestion of *Lactobacillus* species has been shown to decrease development of bladder cancer in a retrospective case-control series from Japan.⁵⁰ In a randomized study of patients with superficial bladder cancer, patients randomized to receive epirubicin instillation plus LC had a significantly lower rate of recurrence at 3 years compared with those receiving epirubicin alone (74% vs 60%, $P = .02$), with no difference in rates of progression or survival.⁵¹

NARROW-BAND IMAGING

Narrow-band imaging (NBI) is an optical technology that employs filtering of white light into 2

narrow bands (440–460 nm and 540–560 nm) that are absorbed by hemoglobin, resulting in visual detection of increased vascularity with tumors. NBI cystoscopy increases detection of tumors resulting in decreased rates of recurrence of superficial bladder tumors.⁵² Unlike other forms of fluorescent-based imaging, NBI does not require instillation of a precursor reagent and only requires a special filter for flexible cystoscopy in the office. In a study of 143 patients, NBI had a greater detection rate for identifying tumors (98% vs 89%, $P = .002$), with similar false-positive detection rates.⁵³ The major drawback with all forms of fluorescent cystoscopy is the high false-positive rate (36%), resulting in increased number of unneeded TURs.⁵⁴ Other drawbacks of NBI include user variability in interpretation of cancer, a learning curve to interpret NBI imaging, and cost of equipment purchase. Herr and Donat followed 126 patients with low-grade tumors using NBI flexible cystoscopy and compared tumor recurrence over a 3-year period in which white-light imaging was used for surveillance. In their study, NBI surveillance resulted in significantly lower rates of tumor recurrence (93% vs 62%, $P = .001$).⁵⁵ Randomized trials are underway to determine the impact of NBI-assisted treatments on bladder tumor recurrence rates.

SUMMARY

As more is learned about the biology and natural history of bladder cancer, office-based management is becoming more widely used for low-grade and -stage lesions. Clinical decision making should be based on risk stratification. Low-risk patients can be safely followed on a semiannual or even yearly basis. Patients with high-risk tumors require more stringent cystoscopic surveillance, cytology, and yearly upper tract imaging. Smoking cessation is an invaluable tool to decrease rates of recurrence, and new technology may aid in detection of recurrence.

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Office-Based Stone Management

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KEYWORDS

• Kidney stone • Anesthetic • Sedation • Endoscopy • Surgery • Lithotripsy

KEY POINTS

- A working knowledge of local anesthetics and conscious sedation protocols is important, as many surgical kidney-stone procedures can be performed without general anesthetic.
- Preoperative urinalysis and culture should be routine for patients undergoing genitourinary surgical manipulation, and overt urinary tract infections should receive a full treatment course of culture-specific antibiotics.
- Shockwave lithotripsy can be performed effectively with conscious sedation.
- If a fragment is known to be left behind or is detected on imaging, knowing its significance will help guide management.
- Postoperative protocols for imaging and second-look nephroscopy are surgeon specific, and can range from no imaging/intervention to routine computed tomography and/or nephroscopy.
- Ureteroscopy has become an indispensable tool for the urologist for both the diagnosis and treatment of benign and malignant urologic conditions.
- Patient selection remains a critically important consideration when determining whether to proceed with ureteroscopy and laser lithotripsy under conscious sedation in an ambulatory setting.

As hospital resources are becoming strained, ambulatory surgical centers and day hospitals are being increasingly utilized. For the urologist, a working knowledge of local anesthetics and conscious sedation protocols are important, as many surgical kidney-stone procedures can be performed without general anesthesia (GA). With any anesthesia, the key goal is to maximize patient comfort while minimizing respiratory depression and avoiding prolonged sedation. When using these medications, a working knowledge of emergency reversal, ventilation (bag mask/laryngeal mask airway/intubation), and cardiopulmonary resuscitation is recommended.

GENERAL CONSIDERATIONS

Endoscopic procedures are typically considered to cause mild to moderate pain when performed under local or sedative anesthetic. Modern rigid and flexible endoscopic equipment is more user friendly and better tolerated by patients. A study from Jeong and colleagues¹ compares various modalities of stone surgery under local anesthetic using a 10-point visual analog scale (VAS). Shock-wave lithotripsy (SWL) reported the most pain (6.62/10); retrograde stenting with rigid cystoscopy (4.48/10), semirigid ureteroscopy + lithotripsy (with preprocedural intramuscular midazolam) (3.18/10), and rigid cystoscopy (3.08/10) all

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caused mild to moderate pain scores. As such, short-acting intravenous opiates and benzodiazepines can be used; however, with proper preoperative counseling, many patients can tolerate selected stone surgery without GA.

Covered in more detail elsewhere, the protocol of the authors' center involves a 6-hour preoperative fast (2 hours for clear fluids) for most procedures that would be considered moderate sedation/analgesia. At this level patients can purposefully respond to verbal commands while maintaining airway patency and spontaneous respirations. Vital signs are taken before, and every 10 minutes (or less) during the procedure in conjunction with continuous oxygen saturations and respiratory-rate measurements, and electrocardiogram tracings (if cardiac risk factors are present). Commonly used medications include benzodiazepines, and short-acting opioids are given parentally. Intravenous access is established for each patient, and bolus doses are preferred, titrating to the level of discomfort and anxiety.

Postprocedural observation is mandatory for a minimum of 60 minutes, and dedicated nursing staff assesses vital signs, sedation, and pain scores before discharge. Patients are instructed in advance that they will not be able to drive and that someone must be present with them at home over the following 24 hours.

Selection for conscious sedation requires a careful assessment of the patient's medical history and surgical issues. Severe systemic disease, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, or difficult airways should all trigger anesthesia's involvement in any planned procedure. The patient's pain tolerance, history of narcotic use, anxiety levels, and specific anatomy should be weighed during consideration for a procedure under sedation. Movement secondary to pain during extracorporeal SWL (ESWL) may reduce efficacy. Similarly, movement during ureteroscopy (URS) could lead to a ureteric perforation, resulting in significant morbidities.

Antibiotics

Preoperative urinalysis and culture should be routine for patients undergoing genitourinary (GU) surgical manipulation. Overt urinary tract infections should receive a full treatment course of culture-specific antibiotics and, if possible, procedures should be delayed until urine cultures are negative.

According to the American Urological Association (AUA) recommendations for preprocedural

antibiotics, cystoscopy with GU manipulation warrants prophylaxis for 24 hours or less, or it should be tailored to risk factors. Fluoroquinolones or trimethoprim/sulfamethoxazole as first-line recommendations are well suited for ambulatory surgery; prescriptions given in advance allow oral doses to be taken by patients 60 minutes preprocedure. Alternative antimicrobials are aminoglycosides with or without ampicillin, first-generation or second-generation cephalosporins, or amoxicillin/clavulanate. Percutaneous surgery also warrants antibiotic prophylaxis of up to 24 hours, with first-line antibiotics including first-generation or second-generation cephalosporins and aminoglycosides (with metronidazole or clindamycin). Second-line agents include ampicillin/sulbactam or fluoroquinolones. Updated in 2008, endocarditis guidelines by the American Heart Association state that prophylaxis for routine GU procedures is not necessary.²

The 2008 AUA recommendation for prophylaxis for all patients undergoing ESWL was recently revisited.³ A meta-analysis of 9 randomized controlled trials involving 1364 patients failed to demonstrate reductions in positive urine cultures, urinary tract infections, or febrile episodes.⁴ A large prospective trial analyzing 389 patients (with only 2% receiving prophylaxis) identified 1 post-SWL urinary tract infection, no cases of urosepsis, and 11 (2.8%) patients with asymptomatic positive urine cultures.⁵ Therefore, with little evidence of benefit, only those with risk factors (advanced age, anatomic abnormalities, poor nutritional status, smoking history, steroid use, immunodeficiency, externalized catheters, colonized urine, distant coexistent infection, and prolonged hospitalization) are now recommended for routine prophylaxis.

CYSTOSCOPY AND STENT INSERTION

Ambulatory cystoscopy can be performed in various settings, including regular procedure beds or dedicated cystoscopy suites with lithotomy-positioning aids with fluoroscopic units and monitors. Undertaken for both the diagnosis and treatment of urolithiasis, procedures can be performed under local anesthetic, regional blocks, or conscious sedation. Flexible cystoscopy, or rigid cystoscopy in women, is considered the least bothersome, and is typically carried out with only topical xylocaine jelly.

Ambulatory ureteral studies can be performed under local or sedative anesthetic, because retrograde/antegrade contrast studies and ureteral stent insertions or changes are procedurally similar to performance under GA. This procedure

may precede SWL in patients with a solitary kidney or large stones. The more complicated procedures, or those involving ureteric manipulation, require careful patient selection and attention to preprocedural pain levels, anxiety, and complicating anatomic or pathologic factors.

Both digital and fiberoptic flexible cystoscopes are available. Modern digital scopes have been shown in several head-to-head comparisons to be favored for their color differentiation in shades of red, contrast, resolution, and fine focusing at varying distances.⁶

Stent Size and Diameter

In determining the ureteric length, Kawahara and colleagues⁷ prospectively measured the ureters of 151 patients using a 5F ureteric catheter. Multiple regression analysis of surrogate measurements for ureteric length identified that the distance from renal vein to ureterovesical junction (UVJ) on axial computed tomography (CT) imaging correlated the most strongly with actual ureteric length. In this study, height and obesity were less strongly associated with ureteric length, as was also seen by Paick and colleagues,⁸ who compared patients' characteristics with intravenous urography imaging. These measurements can easily be performed by noting the slice thickness on the CT study (1, 3, or 5 mm typically), then counting the slices from the renal vein to the UVJ, and multiplying by slice thickness. If, however, a significant amount of tortuosity or redundancy is present, this method will underestimate the length needed.

The authors use 7F double-J ureteric stents, although studies have shown that the diameter of stents does not contribute to symptomology. Distal migration was found more commonly in 4.7F stents than in 6F stents, with no symptomatic or physiologic differences noted otherwise.⁹ If performing stent insertions under local anesthetic, pain has been noted when resistance is met at an impacted stone or high-grade obstruction.¹⁰ If this is suspected, a thinner stent may be preselected, along with verbal instructions as to what the patient may feel when negotiating these areas. However, at times smaller stents composed of softer material may buckle or "accordion" when they reach an impacted stone. In this scenario, a larger or stiffer stent may actually slide by the stone more easily, owing to the increased torsional rigidity.

Analgesia

Inadequate analgesia has been associated with poorer compliance with follow-up flexible cystoscopy in the management of superficial bladder

cancer.¹¹ Regular lubrication or lidocaine jelly can be used to aid in scope insertion. Single-application prefilled disposable syringes help lubricate and dilate the urethra while providing topical analgesia to the patient. Penile clamps are used by some to stop backflow while increasing the dwell time for the topical anesthetic to take effect.

A meta-analysis from 2009, comparing 4 randomized trials measuring pain during flexible cystoscopy, showed a significant improvement in moderate pain levels when using 2% lidocaine jelly.¹² Three of the 4 studies showed no difference, yet a significant advantage was found when patients were pooled with a fourth, larger study. Another meta-analysis including 3 additional studies with less severe pain thresholds also failed to demonstrate a clear advantage.¹³

Intravesical lidocaine instillation has also been described as both a therapeutic and a diagnostic tool. Used to help differentiate patients with chronic bladder pain from those with pelvic pain, it has been used by some centers to supplant hydrodistention.

Watching the procedure on the video monitor has shown mild improvements in perceived pain levels and, rarely, worsened discomfort.^{9,14,15} Kobayashi and colleagues¹⁶ comment that improved outcomes in their patients were noted if verbal instructions were given to patients, based on when the scope was being inserted and when they were about to traverse the membranous urethra.

Male Versus Female

The short urethra of females makes rigid cystoscopy more accessible, and potentially less painful, than in men. A study comparing VAS pain measures during cystoscopy in women showed similar ratings between flexible (1.4/10) and rigid cystoscopes (1.6/10).¹⁷ Older women may have less sensation, but more friable and delicate mucosal surfaces.¹⁸ Vaginal atrophy can lead to lacerations and bleeding if care is not used in manipulation. The urethral meatus can also be difficult to locate and intubate in postmenopausal women. Atrophy leads to the meatus being displaced posterior to the pubis, requiring blind intubation using the rigid sheath and the obturator (or flexible scope) to reduce trauma.

In men, a significant reduction in postprocedural symptomatology was found 1 week after local anesthetic and flexible cystoscopy (33%), compared with rigid cystoscopy under GA (76%).¹⁹ Of patients who have had previous rigid cystoscopy under GA, only 11% preferred it to flexible cystoscopy under local anesthesia.²⁰

Procedure

When rigid cystoscopy is performed on women selecting the sheath of smallest diameter, using adequate lubrication with minimal bladder distention are important in minimizing pain. Room-temperature irrigation, warmed skin-preparation solution, proper draping, and fluid drainage maintain patient comfort and thus reduce anxiety levels. Draping for sterility while protecting patient modesty and ensuring irrigation drains away from the patient will improve comfort and minimize movement. Water-based lubricant is instilled at the meatus before scope insertion to provide urethral dilation and comfortable passage. To minimize discomfort, the authors enter the bladder with the assistance of the blunt obturator and use the 70° lens to visualize the entire bladder with minimal torque.

Women may be placed in lithotomy (for rigid) or frog-leg position for flexible cystoscopy. If hip pain or contractures limit articulation, padding may be used to support the knees in a frog-leg position, or the most flexible leg can be bent (with the surgeon moving to that side of the bed). Both legs can also simply be adducted, or low lithotomy may be more comfortable for some. The meatus can be visualized using the light from the scope to help illuminate the area. If not seen, palpation can help locate its position (typically deviating posteriorly with atrophic vaginitis) while using the other hand to introduce the scope tip. The female urethra angles anteriorly, and can be visualized best when coming out of the bladder with irrigation fully open.

In men the foreskin is retracted and the penis is gripped laterally just proximal to the coronal sulcus, and held on stretch at 45°. The scope tip is introduced after saline irrigation has bled the air out of the system, keeping the lumen centered as the scope is advanced. At the level of the external sphincter, a verbal warning that a pinching sensation may be experienced is important.¹⁶ One study documented that a transient increase in irrigation pressure (by squeezing the irrigation bag) hydrodistends the sphincter, decreasing pain (3.0–1.38/10) when passing a flexible scope through the membranous urethra.²¹ Once past the sphincter, anterior flexion allows passage through the prostatic urethra and into the bladder.

A systematic evaluation of the bladder will keep any abnormality organized, especially if multiple lesions are present. Dividing the bladder into anterior, posterior, right/left lateral, and trigone will help organize findings for communication with the patient and documentation. Full retroflexion of the scope will help evaluate the median

lobe and the bladder neck. Testing deflection before insertion of the scope will help ensure the scope is not damaged, and confirms which direction of angulation has the greatest deflection. If a high bladder neck precludes the scope being deflected adequately to assess the trigone, rotating the entire scope 180° to have maximal deflection posteriorly may help improve visualization.

Stent Insertion

Most retrograde double-J stent insertions in North America are currently done under GA using fluoroscopic guidance. Stent insertions can also be done under conscious sedation (CS) or local anesthetic, and is well tolerated in many patients.

Acutely obstructing stones may also be stented under local anesthetic, as described in a retrospective review of 46 patients. Rigid or flexible cystoscopy was used to introduce a Sensor guide wire (Boston Scientific) up to the level of the kidney, then a retrograde pyelogram performed through a 5F open-ended catheter. A 6F double-J was then placed (without tether), and postprocedural radiographs were used for confirmation of position. Failures (5 under local anesthetic) were due to inability to position a wire or stent because of stenotic ureteric orifice or impacted stones, and inability to find the ureteric orifice, while 1 procedure was terminated owing to the patient's discomfort. One stent was malpositioned under GA yet, even accounting for these discrepancies in failure, the cost was 3 times greater on average in the GA group (\$30,000 vs \$11,000).¹⁰

Jin and colleagues²² compared ureteric catheter placement via rigid and flexible cystoscopy (under local anesthetic), finding the latter to afford better comfort in men (VAS: 7.2/10 vs 3.5/10) and lower gross hematuria rates (8.6% vs 25%), with no difference in procedural times. There was no significant difference in the number of successful intubations or in pain levels experienced by women. Though not equivalent to stent insertion, this study does highlight the role of flexible cystoscopy in minimizing morbidity while facilitating intubation of the ureteric orifice.

Stenting without fluoroscopy has also been described, and is often required in situations where patient transfer or radiography are not available (ie, the intensive care unit). A retrospective analysis of a nonfluoroscopy stent-placement technique was found to have equal outcomes and complications in comparison with standard stent placement.²³ In this study, stent placement without fluoroscopy was performed after ureteroscopic stone removal, when the length of the ureter can be measured from the

ureteropelvic junction to the UVJ. This distance is then measured on the stent from the proximal curl, and marked on the distal aspect. The wire is then back-loaded through a cystoscope and the stent inserted until the mark has advanced into the ureteric orifice. The wire is then withdrawn 10 cm, and the cystoscope backed out until it is 1 cm distal to the bladder neck. The stent is then released when the most distal tip is visualized, and placement is confirmed by assessing the curl directly.

This technique is only applicable when there is no ureteric obstruction, and length of the ureter is measured with a ureteroscope. This procedure can be helpful in reducing radiation doses in those with significant previous exposures, younger patients, and pregnant women. For most patients, using fluoroscopy while minimizing exposures will facilitate proper stent placement without having to subject the patient to ureteroscopy. As an alternative, ultrasonography can be used to monitor the placement of the guide wire, followed by monitoring the coiling of the renal end of the ureteral stent.²⁴

Post-Stent Insertion Symptomatology

Discomfort after stent insertion and understanding of the procedure may be poorly addressed; for this reason written material can help alleviate patients' uncertainties, potentially minimizing the need for emergency phone calls and assessments.²⁵ The use of as-needed medications can help significantly reduce flank pain and lower urinary tract symptoms caused by refluxing urine and stent irritation. Nonsteroidal anti-inflammatories (NSAIDs), anticholinergics, pyrimidine, and α -blockers can be used alone or in combination.

A randomized placebo-controlled trial comparing pyrimidine and extended-release oxybutynin showed no difference in bothersome symptoms in stented patients between the medication and placebo arms²⁶; however, the sample size of this study was small. α -Blockers have been used to help relax ureteric smooth muscle contractions and trigonal spasms. Several studies have prospectively examined the use of α -blockers in stented patients and their effects on urinary tract symptoms, quality of life, and pain.^{27–35} Two meta-analyses have been performed, including up to 12 trials, all of which showed significant improvements in the Ureteral Stent Symptom Questionnaire and pain scores.^{36,37}

Recently a randomized controlled trial comparing tamsulosin (0.2 mg daily), solifenacin (5 mg daily), a combination of both, or no

medication was performed. International Prostate Symptom Score and pain scores were used, and combination therapy significantly improved both irritative and obstructive symptoms.³⁸

SHOCK-WAVE LITHOTRIPSY

Anesthetic Considerations

GA, epidurals, paravertebral blocks, CS, and topical analgesia have all been used in ambulatory ESWL. The first 3 modalities require involvement of and monitoring by dedicated anesthesia staff, and have varying lengths of recovery.³⁹ Epidural blocks tend to have longer lag times than modern short-acting anesthetic agents.⁴⁰ Subcutaneous and intramuscular injection of short-acting (lidocaine) and long-acting (ropivacaine) local analgesics have been studied, and show improvements in pain if administered over the correct area of shock-wave focus, sparing patients the need for systemic agents.⁴¹

Specific lithotripsy units and characteristics of patient (body habitus, spinal deformations, anxiety, baseline pain tolerance, and so forth) will dictate the pain experienced. Type and position of stones, renal anatomy, and the need for adjunctive procedures (stenting, ureteroscopy, and so forth) must be considered when triaging for GA versus CS. The Hounsfield units (HFU) of stones on unenhanced CT scans may also help predict which patients are better suited for SWL than for endoscopic treatment. In a study reviewing the outcomes of 50 patients with stones smaller than 1 cm undergoing SWL, it was found that stones with HFU greater than 900 had significantly worse stone-free rates than those with HFU of less than 500.⁴²

Several studies have implicated that the modality of anesthesia may affect SWL outcomes. Lee and colleagues⁴³ showed outcome differences were greatest in upper pole stones; however, there was no difference in stones 10 mm or smaller with use of either GA or CS. Zommick and colleagues⁴⁴ found equivalent efficacies, while GA was slower and required less fluoroscopy time. Though somewhat contradicted by other retrospective series, one has to consider that modality may play a role in the final outcome of stone treatment.⁴⁵

Topical lidocaine/prilocaine cream (EMLA) has been investigated, and has decreased intraoperative analgesic sedation, improved fragmentation, and decreased patient movement, although it is not effective enough to mitigate the use of intravenous sedation.^{46,47} A 3-armed study investigating pain control using preoperative NSAIDs versus morphine versus EMLA showed no

significant differences in pain score, and no increased risk of hematoma or hematuria.⁴⁸ NSAIDs are commonly used for renal colic, and, lacking gastrointestinal side effects, COX-2 inhibitors may carry a renoprotective effect after SWL, as demonstrated by Park and colleagues⁴⁹ in a mouse model. A meta-analysis of 3 randomized controlled trials using NSAID analgesia in modern ESWL therapy showed significant pain reduction equivalent to that seen with opiates.⁵⁰

Several randomized trials investigating a combination of auditory and visual distraction during lithotripsy have noted improvements in the extent of pain and distress of patients.^{51–53} Providing self-selected music and/or video has been shown to reduce anxiety, pain scores, and analgesic requirements. Music can be facilitated by providing headphones, isolating the patient from the ambient noise of the lithotripsy suite (even before entry), along with a portable video monitor on an adjustable stand. Once positioned on the lithotripsy table, adjusting the monitor prevents neck strain, and subsequent movement is avoided. Simply providing ear plugs has also been shown to reduce the amount of propofol required during SWL.⁵⁴

Each lithotripter will have unique peak pressures, focal area at skin level, and focal zones, in addition to settings required to fragment stones (number of shocks, energy settings, and duration of treatment). Just as important as understanding the equipment settings is ensuring efficient delivery of the shock waves (SW), which can be significantly affected by coupling issues. To ensure maximal energy transfer from the treatment head to the patient, coupling the two involves using a gel or oil medium. This medium should be similar in density to soft tissue, without air bubbles, yet viscous enough to adhere to both body and treatment head. A study quantifying the air-bubble content of coupling media found that maximal phantom stone fracture was provided by a silicone-based lubricant, and ultrasound gel in which the bubbles had been removed. With media including more air, the efficacy of the SW diminished.⁵⁵ When the surface area of the air bubbles was quantified, 2% coverage of the treatment head by bubbles reduced stone breakage by 20% to 40%.⁵⁶

To effectively deliver a shock wave from the treatment head to the stone, the pulse has to travel through fairly homogeneous materials. Heavier coupling agents such as petroleum jelly may negatively affect wave transmission.⁵⁷ Ensuring initial and continued contact with the treatment head preserves a maximally air-free transition. When a patient moves, breaking the seal and recoupling

without readministering the medium decreases peak pressures by 37% and decreases energy transmission 57%, in turn requiring more shocks for the same stone. Applying liberal amounts of gel to the treatment head and raising the unit to meet the patient's back will initially ensure minimal formation of air bubbles.⁵⁶ The patient should be positioned with care before coupling; however, if there is a need for repositioning or the patient decouples, the application process should be repeated.

Imaging

Fluoroscopic guidance during lithotripsy is standard for most units, although in-line ultrasound probes are now becoming readily available. The urologist should be aware of the radiation risk, and take an active role in minimizing exposures. Judicious use of radiation time, positioning the intensifier closer to the patient, standing away from the fluoroscopy head, using last-image hold, and reducing the pulse rate from 30 frames per second (FPS) to 15 fps help reduce total radiation exposure. In addition to surgeon experience,⁵⁸ employing experienced technologists has also been shown to improve outcomes while reducing fluoroscopic time.⁵⁹

Radioopaque stones in the kidney and ureter are located just as for any endoscopic procedure; however, F2 is defined by rotating the C-arm to judge the stone's 3-dimensional positioning. This action can be taken purely fluoroscopically or in conjunction with ultrasonography, which may be used to further reduce radiation (ie, in children) or for radiolucent stones. Without ultrasonography, intravenous contrast can be given safely as a bolus or drip infusion to identify filling defects, or retrograde pyelography can be performed.^{60,61}

Complications

Anesthetic modality has not changed the risk of complications from SWL. Although there is a theoretically reduced risk of complications of GA from avoiding intubation, no study has been large enough to demonstrate such trends. Hematoma, hematuria, flank pain, skin bruising, ureteric obstruction, urinary tract infection, and sepsis are all possible. Rates of perinephric hematoma range from 1% to 8% with current-generation lithotripters, and a case-matched review of 6172 SWL treatments showed intraoperative hypertension and anticoagulation/antiplatelet use to significantly increase its risk.⁶² Almost all can be managed conservatively, without requiring transfusions or additional procedures.

SWL Settings

In controlling the rate and energy levels, several strategies have shown benefits in efficacy and morbidity. In attempts to improve shock-wave delivery, modern machines have increased power ranges, higher peak pressures, and smaller focal zones. Although this has led to greater patient comfort with less focused energy at the skin level, greater hematoma rates and lower stone-free rates have been noted in comparison with the earlier Dornier HM3 lithotripter.⁶³ Delivering the fastest rate at the highest power for the maximal number of shocks⁶⁴ may intuitively improve fragmentation, anesthetic times, and energy delivered, but does not necessarily improve outcomes.

Energy

Priming kidneys with a lower energy level (12 kV) for 100 to 500 shocks, before delivering the balance of 2000 SW at full power (24 kV), was shown to have protective effects with regard to hemorrhagic lesions when tested in porcine models.⁶³ Whether these priming shocks are given with a 3-minute pause or over a period of approximately 4 minutes, they confer the same benefits, resulting in subsequent treatment-dosed SW being less damaging.⁶⁵

Several clinical studies have approached stepwise protocols for SWL in terms of stone comminution, complications, and functional renal outcomes. The first randomized trial allocated 25 patients to 3000 shocks of escalating energy (starting at 11 kV, increasing by 1 kV every 500 SW to 13 kV), compared with a fixed protocol (13 kV).⁶⁶ Stone-free rates were slightly improved, with smaller fragments being produced by energy escalation, and with no differences in complication rates. In 2010, 45 patients underwent escalating (500 SW at 14 kV, then 1000 SW at 16 kV, then 1000 SW at 18 kV) or fixed-energy protocols (2400 SW at 18 kV) with gated rates between 60 and 80 shocks per minute (spm) using the Dornier DoLi-50 lithotripter.⁶⁷ Although patients received less total energy in the stepwise arm, they showed better stone fragmentation on 1-month follow-up radiography, and renal injury (assessed by urinary b2-microglobulin and b2-macroglobulin excretion) was significantly reduced, with no significant differences in complication rates.

Rate

In addition to optimizing energy the rate has been studied, generally showing better results with slower shock-wave rates. This finding may be

due to faster rates leading to decreased wave transmission, decreased negative pressure components, and less efficient formation of cavitation bubbles.^{68,69}

Assessing the conventional 120 spm in comparison with 60 spm, a randomized trial showed improved successful fragmentation for stones larger than 10 mm (44% vs 10.8% fragments <4 mm).⁷⁰ For all stones, stone density predicted successful fragmentation, whereas for those larger than 10 mm, density, stone size, patient age, and 60 spm were all significant predictors. No differences in pain, complications, or urinary markers for renal injury were noted, although there was an increase in fluoroscopic time. This rate decrease effectively doubles the treatment time, as a similar number of shocks were delivered in both arms. Several other protocols have been tested, showing that slower rates improve fragmentation, reducing the need for auxiliary procedures without increasing complications. A case-controlled study⁷¹ compared rates of 70 spm and 100 spm, with stepwise energy increases (for both groups) and follow-up imaging at 6 months. The slow-rate group required fewer total shocks in this study (3045 vs 4414; $P < .001$), had improved stone-free rates (67% vs 25.25%; $P < .001$), and had reduced retreatment rates (21.6% vs 45%; $P = .013$). Hospital Costing Department information determined a 50% cost reduction in the slower-rate group (£497 vs £1002, $P = .001$).

SECOND-LOOK PERCUTANEOUS NEPHROLITHOTOMY

Percutaneous nephrolithotomy (PCNL) is now the preferred procedure in patients with large renal stone burdens. Performed mostly under GA in the prone position, stone-free rates from 40% to 95% have been reported, depending on many factors relating to the patient's anatomy, stone burden, stone composition, and surgical expertise.⁷²

Ideally a CT scan is available for surgical planning to assess stone burden, renal anatomy, and adjacent structures. Before completion, visual and fluoroscopic survey of all calyces, renal pelvis, and ureter minimizes the risk of leaving significant fragments. However, this is not always possible because of bleeding and poor visualization, hemodynamic instability under GA, sepsis, and so forth. In these cases residual fragments may not be fully appreciated, and even if identified may not be immediately extractable.

If surgery is terminated before completion, or if one is uncertain of the size, number, or location

of remaining fragments, postoperative imaging is helpful. Kidney/ureter/bladder radiographs or CT studies are commonly used on postoperative day 1, whereas ultrasonography is technically difficult because of in-field dressings and drainage tubes.

Natural History of Residual Fragments After PCNL

If a fragment is known to be left behind or is detected on imaging, knowing its significance will help guide management. In a study by Raman and colleagues,⁷³ postoperative CT scans showed residual fragments in 8% of their PCNL cases; 47% of fragments were lower pole, 32% intrapolar, 24% upper pole, and 18% pelvic/ureteric stones. Sixty percent of fragments were smaller than 2 mm and 79% were smaller than 5 mm. All of these patients were treated conservatively, and over the following 32 months 43% required medical care, 61% of whom underwent surgical intervention. Factors predicting fragment-related events were fragments larger than 2 mm and location within the pelvis or ureter.

Assessing economics of expectant management and second-look PCNL, fragments smaller than 2 mm did not warrant routine second looks, as the added cost of the procedure (US \$2475) outweighed the cost of expectant management (\$690). Stones 4 mm or larger had higher associated costs with expectant management (\$4672) owing to the increased percentage of patients who required medical attention/secondary procedures, making second-look nephroscopy economically advantageous in these patients.⁷⁴

Given the belief that any residual fragments in children are significant risks for future stones, Roth and colleagues⁷⁵ reported that stone-free goals may be accomplished with second-look and third-look nephroscopy. Stone-free rates were 46% after initial PCNL, 86% after the second look, and 97% after third-look nephroscopy. Children, however, had all procedures completed under GA, and 2 patients required a second placement of renal access.

Postoperative Drainage

On deciding to terminate a case that may require a second-look nephroscopy, it is important to determine whether the same access is adequate. If so, it is imperative that this tract be maintained until the second-look procedure is possible. If the tract is maintained, ureteric access allows straightforward placement of a safety wire. Clinical situations may dictate one's choice of drainage tubes. Brisk bleeding may necessitate a large-

bore catheter for balloon tamponade while multiple accesses may allow for placement of a loop nephrostomy tube. Nephroureteral catheters (with both bladder and renal pelvis curls) may be used to help minimize accidental displacement and maintain ureteric access. If external drainage is not necessary, a straight 5F ureteric catheter may be advanced antegradely to the distal ureter, suturing the free end at skin level and tucking the excess under a dressing. As long as a clear tract exists from skin to collecting system, the size of the nephrostomy tube does not affect the accommodation of a nephroscope if the second-look procedure is performed within several days.⁷⁶

Intraoperative/Postoperative Imaging

At the completion of each case the scope should be removed, and on high magnification the kidney should be observed fluoroscopically, manipulating the sheath to ensure it is not obscuring any fragments. If there were initially stones in the calyx entered, the sheath should be backed out under direct vision while inspecting for fragments.

Postoperative protocols for imaging and second-look nephroscopy are surgeon specific, and can range from no imaging/intervention (especially in tubeless techniques) to routine CT and/or nephroscopy. CT scans provide information on residual stone burden, hematoma formation, and renal anatomy. Stone dust may be overcalled by CT, and timing may be important because fragments found immediately after surgery may wash out over time.⁷⁷ Therefore, it is important to correlate preoperative and postoperative imaging with intraoperative knowledge of what was fragmented and what may have been left behind. The negative predictive value of fluoroscopy + endoscopy is 100% for fragments 4 mm or larger, 88% for fragments from 2 to 4 mm, and 73% for the smallest fragments. Consequently, more than a quarter of cases that were deemed stone-free at the time of surgery had fragments 4 mm or smaller.⁷⁸

The radiation dose is an important consideration, and should be considered for each patient based on intraoperative findings, gender, age, total number of previous scans, and patient preference. Once a CT scan is performed, the stone burden should be considered based on its risk of passage, possible future need for surgical intervention, risk for future stone growth, patient preference, and technical feasibility via URS, PCNL, or SWL. Routine CT scans can avoid second-look procedures, as only 80% of cases whereby the surgeon believed there were residual stones had stones confirmed on CT. This finding implies that routine CT in patients thought to have residual

fragments may reduce second-look procedures in 20% of cases.⁷⁸

Timing

Second-look procedures have been typically performed between 48 and 72 hours postoperatively, the average length of stay being 3.7 days.^{75,79} Postponing a second look until hematuria resolves will optimize visibility. If a patient is febrile or shows signs of sepsis, a second procedure should be delayed for 24 hours until the patient is stable and afebrile. Patients with indwelling nephrostomy tubes who are discharged home and brought back after several weeks will have mature tracts; however, unless a large-bore tube is in place, dilation of these tracts will likely be required.

Preprocedure Preparation

In attempting second-look nephroscopy consent should be obtained, clearly outlining any complications that may be encountered. Common morbidities include bleeding/hematuria, infection, discomfort/pain with manipulation, conversion to GA, and need for additional procedures. Hydrothorax is also possible in supracostal access, and may necessitate the placement of a chest tube.

There is no standard approach to second-look nephroscopy; although most surgeons position the patient prone or flank, a posterior approach to patients sitting upright has been described. A Foley catheter is required because of the quick accumulation of irrigation. Scout images and nephrostograms can be acquired to highlight radioopaque stones, renal anatomy, and filling defects. Residual clots may cause filling defects, and retained contrast or sand may appear as radioopaque densities on fluoroscopy, requiring visual inspection. If postoperative imaging is sufficient and residual stones are straightforward with a ureteric-access catheter in place, fluoroscopy can potentially be omitted. In these cases careful inspection of each calyx should be performed, and all stone fragments removed must correlate with post-PCNL imaging to ensure completeness.

Depending on the type of nephrostomy tube present, a safety wire is inserted to the level of the bladder if possible, or curled in the renal pelvis. This maneuver is easily performed when nephroureteral catheters, reentry Malecot nephrostomy tubes, or open-ended ureteric catheters are placed during initial surgery. If only renal drainage is present, a combination of Bentson guide wires (Cook Medical) and straight/angled Glide wires (Boston Scientific) can be used in

addition to Kumpe (Cook Medical) or straight/angled Torque catheters (Boston Scientific). Fluoroscopy is then used to guide the wire down to the bladder, and the free end is fixed to the drapes. If a mature tract is present a safety wire may not be necessary to enter the kidney; however, to prevent loss of access while maintaining the ability to place a stent or nephrostomy tube quickly, the authors use a safety wire when working in the upper tract.

Other equipment to have on hand includes an assortment of tipless baskets based on residual stone size. A flexible cystoscope is the main scope used during most second looks, and a flexible ureteroscope can be used for nephroscopy and antegrade ureteroscopy. A Holmium laser with a 200- and 365-mm fiber should be present, in case fragments are too large to be pulled out in one piece. A 365-mm fiber will be adequate for the flexible cystoscope, but is too large for flexible ureteroscopy. Using a semirigid ureteroscope next to, or even through the nephrostomy tube has been described, but requires fragments to be relatively small and in a straight line from the entered calyx.⁸⁰ A rigid nephroscope, graspers, and dilation instruments (balloon or rigid) should be available, yet will rarely be used under CS. Stents and nephrostomy tubes predicted to be needed at completion should be present to minimize delays in case closure.

With the nephrostomy tube removed, redilation and sheath placement are rarely required when using a flexible nephroscope. Irrigation is initially maintained at approximately 60 mm H₂O, then adjusted based on visualization. The flexible scope can be introduced next to a safety wire or over a second wire. Once in the collecting system, clots may be present and adherent to mucosa and stones. Hooking up suction tubing to the instrument port allows intermittent irrigation and suction as necessary. Irrigating and grasping clots with endoscopic baskets may reveal associated fragments that are simultaneously removed.

Sheath insertion is not always necessary, but may be helpful in select situations. If the tract is difficult to navigate with a flexible instrument and multiple passes are required, a 24F sheath may be used. Bleeding from the tract will reduce visualization, and inserting the largest sheath size tolerated will minimize blood in the field while maximizing drainage. A reported series of routine second-look nephroscopy without sheaths discovered that 5% of supracostal accesses resulted in hydrothorax requiring chest-tube insertions. This situation prompted the investigators to routinely use sheaths in all supracostal nephroscopies.⁷⁹

Small stones can be removed via extraction of endoscopic baskets. Nitinol tipless baskets allow for negotiation within tight spaces. Time to extraction has been shown to be quickest for stones smaller than 5 mm using the Halo basket (Sacred Heart Medical), and for larger stones using the Zerotip basket (Microvasive).⁸¹ Care should be taken to ensure the stones are seated securely in the basket, ensuring they are not lost within the tract during extraction. When a sheath is not used, fragments remaining in subcutaneous or perirenal tissue could become a source of chronic irritation and infection, and may confuse future imaging.

Laser litholapaxy can be performed during ambulatory nephroscopy. Under CS, involuntary movements, along with renal excursion secondary to respirations, may lead to a challenging environment, increasing the risk of mucosal injury and perforation. Starting at 6.4 W (0.8 J/0.8 Hz) using a flexible nephroscope and 365- μ m fiber (or a 200- μ m fiber if severe angulation is required), the goal is to fracture large pieces until they are removable by basket.

“Popcorning” fragments is difficult in this setting, as it requires steady laser positioning near a stone to cause fragments to bounce and make repeated contact with the laser. However, if stones are within a large hydronephrotic calyx with a narrow infundibulum, popcorning these stones can be helpful, as fragments are trapped and pieces need to be fairly small to be pulled through the infundibulum. Incision or dilation of stenotic infundibulum during an ambulatory procedure is not recommended, owing to the risk of bleeding and pain.

Gentle antegrade flexible ureteroscopy with laser litholapaxy and basket extraction may also be performed. Several studies have shown that patients tolerate retrograde semirigid and flexible ureteroscopy under local or sedative analgesia without increased morbidity or decreased rate of efficacy.^{82,83} If a large volume of stone is present and manipulated during the session, antegrade ureteroscopy will ensure the ureter is stone free. Sand and small fragments can be washed down to the bladder using the ureteroscope. If gravity irrigation is used for nephroscopy and stones are not fragmented, or if the ureter is previously stented, the risk is reduced on wash down. In cases involving steinstrasse or large ureteric stones, GA should be considered during second-look procedures.

Placement of a ureteric stent and nephrostomy tube at the completion of second look are facilitated by having a safety wire in place, although most patients may not need either. Antegrade stenting is best performed with fluoroscopy (to assess the distal curl) and through or beside a

flexible nephroscope. If performed through the scope the wire has to be back-loaded into the working channel, and pushers supplied with stents are not of adequate length. In these situations a 5F open-ended catheter can be used to advance the stent to the correct position while confirming that the curl is in the renal pelvis. Stent graspers may be needed if the stent is not placed in the correct position. Advancing the stent alongside the flexible nephroscope can be tricky, as it can be challenging to stabilize the wire and stent if they buckle without a working sheath.

URETEROSCOPY

Ureteroscopy has become an indispensable tool for the urologist for the diagnosis and treatment of both benign and malignant urologic conditions. Although the bulk of ureteroscopy is still performed in an operating-room setting under GA, a role for office and ambulatory procedures with either local anesthesia only, or combined local anesthesia with moderate sedation, in select patients has developed. In these patients the ambulatory setting may provide more convenient care in a cost-effective environment that is easy to access.

Diagnostic Procedures

Jones and Stroom⁸⁴ first reported office-based cystoureteroscopy using a flexible cystoscope in a select group of patients who had undergone a prior distal ureterectomy and had a patulous neo-orifice. Only intraurethral lidocaine was used, and patients tolerated the procedure well. Visibility was deemed excellent.

Subsequently Reisiger and colleagues⁸⁵ reported their experience with anesthesia-free ureteroscopy in the office in the surveillance of patients who had undergone prior endoscopic treatment of upper-tract urothelial cell carcinoma. Of note, these patients had all undergone prior “unroofing” of this distal ureter, which facilitated passage of the ureteroscope in the office.⁸⁶ These procedures were performed in the office and were well tolerated by the patients, with 65 of 67 (97%) having a complete survey of the collecting systems including the lower pole. Fluoroscopy was not used, but a prior retrograde pyelogram served as a template of the collecting system. The investigators note that initially they selected patients who had significant anesthetic risk factors for the office-based procedure, but with increasing experience it was offered to a wider range of patients in an effort to reduce cost, time, and inconvenience to patients. Office-based upper-tract surveillance seems a viable option for patients with a history of transitional cell carcinoma.

Ureteral Stones

Indications and technique

Patient selection remains a critically important consideration when determining whether to proceed with ureteroscopy and laser lithotripsy under CS in an ambulatory setting. Patients with a history of sleep apnea, history of difficult intubation, American Society of Anesthesiologists (ASA) physical class score of III or higher, and chronic narcotic use are typically managed with general or regional anesthesia in the operating room.

In men, primarily distal stones are considered for ambulatory procedure under CS, whereas in women mid and distal stones are considered. Although no strict cutoff in terms of size is used, clinical judgment is necessary in selecting patients. In general, solitary stones 8 mm or smaller are considered.

Hosking and Bard⁸⁷ first reported the treatment of small (≤ 5 mm) distal ureteral stones under intravenous sedation with fentanyl and midazolam in 1996. Using a small 6F rigid ureteroscope, they were able to basket-extract the stones successfully in 67 of 70 patients (68 patients had distal stones and 2 were in either the middle or upper third) in a safe fashion. A follow-up study in 2003 compared ureteroscopic stone removal with ESWL, both under CS, for the management of distal ureteral stones.⁸⁸ The investigators reported that women tolerated distal URS equally with ESWL, whereas men showed a preference toward ESWL. However, treatment success was higher with URS, at 95% versus only 72% in the ESWL group. In an environment where ESWL had primarily been used for these patients, this technique now provided an attractive, cost-effective alternative.

Subsequent work has demonstrated that ureteroscopy with pneumatic or laser lithotripsy can be safely performed under CS. Rao and colleagues⁸⁹ administered diclofenac sodium (75 mg) and promethazine hydrochloride (12.5 mg) 30 minutes before the procedure, then sedated patients with a combination of fentanyl and midazolam at the initiation of the ureteroscopy with lithotripsy. Of their patients, 87.10% deemed the procedure acceptable and only 4.84% reported the procedure as painful. Success rates were highest for distal stones at 97.30%, with 86.66% for upper and 80% for mid-ureteral stones.

Anesthetic considerations

At the authors' institution (The Ohio State University Wexner Medical Center), physicians administering moderate conscious sedation must be first accredited by the institution. This process involves

completing a hands-on airway course, demonstrating competencies through computer-based learning modules, and being Advanced Cardiovascular Life Support (ACLS) certified. Nurses, also ACLS certified, administer the medications as directed by the physician and monitor the patient during the procedure. Monitoring includes continuous pulse oximetry, cardiac rate and rhythm assessment, intermittent blood pressure monitoring, and assessment of the relative degree of patient comfort. Patients are administered promethazine hydrochloride, 12.5 mg intravenously, in the preoperative holding area to reduce nausea at the time of the procedure. Oxygen via nasal prongs is used during the duration of the procedure. Once positioned in the procedure area and the surgical time-out is completed, the patient is sedated with a combination of fentanyl and midazolam. Typically 2 mg midazolam and 100 mg fentanyl are used to start the procedure. The patient's response to this dose is evaluated. If the patient is not adequately sedated, or if discomfort is noted during the procedure, additional aliquots of 50 mg fentanyl and 1 mg midazolam are administered. A maximum of 500 mg fentanyl and/or 5 mg midazolam are used. The ratio of fentanyl to midazolam is somewhat individualized. For patients who report primarily pain, a greater ratio of fentanyl to midazolam is used; conversely, if patient anxiety is the primary concern, the ratio of fentanyl to midazolam is reversed. After the procedure is complete, patients are monitored in the postprocedure recovery area for approximately 1 hour until discharge criteria are met.

Technical considerations

Once the patient is adequately sedated, a flexible cystoscope is used to pass a hydrophilic guide wire up the ureter on the affected side. Fluoroscopy is used to confirm the guide-wire placement and the cystoscope is removed. The bladder is then emptied with a 16F straight catheter. An 8F to 10F coaxial dilator is then carefully passed and used to dilate the distal ureteral orifice. Often, a distal stone can be felt as the dilator passes up to it. The 8F to 10F coaxial dilator is then removed. A 7F or smaller semirigid ureteroscope is then carefully passed via the urethra into the bladder and into the distal ureter. The combination of the dilation with the 8F to 10F dilator and the 7F (or smaller) ureteroscope make balloon dilation rarely necessary. The ureteroscope is then carefully advanced alongside the guide wire until the stone is reached. If there is difficulty reaching the stone, such as from ureteral edema, a second hydrophilic guide wire can be passed

through the working channel of the ureteroscope to help guide the scope to the target. Once the stone is reached, the guide wire in the working channel is removed. If the stone is very small, basket extraction with a nitinol stone basket may be performed; however, if there is any concern that the stone is too large to easily extract, the authors strongly recommend first fragmenting it with a Holmium:YAG laser. An optical fiber of 365 mm core size is loaded through the working channel and the stone is targeted. Pulse-energy settings of 0.6 J at 6 Hz are used initially and then increased slightly up to 1.0 J at 10 Hz, depending on how hard the stone is. Higher pulse-energy settings increase the degree of stone retropulsion, so using as low a setting as possible that effectively fragments the stone is recommended.⁹⁰ Once the fragments are broken into pieces small enough to extract, the nitinol basket is used to pull the fragments out of the ureter. To limit the risk of trauma to the urethra from passing the semirigid ureteroscope in and out, the majority of the fragments are deposited in the bladder. On the last pass, a fragment is captured and removed, and sent for biochemical stone analysis.

The authors do not routinely place stents after uncomplicated semirigid ureteroscopy. After the ureteroscope is removed, a retrograde pyelogram is performed through a 5F open-ended catheter. Pulse fluoroscopic images are obtained. If there is no extravasation and if contrast appears to be draining briskly down to the bladder, a stent is not placed. However, if the procedure has been complicated, such as from an impacted stone, perforation, ureteral injury from the laser, or other similar concerns, a stent should be placed at the completion of the procedure.

At present, the authors' practice is to treat most upper ureteral and renal stones in the operating room. With the use of a ureteral access sheath and liberal basketing of stone fragments, the use of a GA is preferred.

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Office-Based Anesthesia for the Urologist

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KEYWORDS

- Office-based anesthesia • Office-based surgery • Patient safety • Non–operating-room anesthesia
- Preoperative evaluation • Postoperative nausea and vomiting • Postoperative analgesia
- Recovery from anesthesia

KEY POINTS

- Advances in surgical techniques coupled with the development of faster-acting, safer anesthetics allow for more invasive procedures to be performed in an office setting.
- Economic demands to decrease health costs and patients' preference for the nonhospital setting also have contributed to the growth of office-based surgery (OBS), and will continue to fuel its growth in the future.
- It is imperative that we continue to strive to hold the OBS centers to the same standards as ambulatory and hospital settings with regard to patient safety.
- Anesthesia for OBS should be such that the patient recovers quickly with few side effects or pain, and has a timely discharge.

INTRODUCTION

Office-based anesthesia (OBA) is defined as the provision of anesthesia services in an operating or procedure room that is not accredited as an Ambulatory Surgery Center (ASC) by the state in which it operates and is integrated into the day-to-day operations of a physician's office¹; that is, anesthesia and surgery are being performed in an office setting.

Office-based surgery (OBS) is on the increase. In 2005, 25% (10 million) of all elective procedures performed in the United States were performed in an office setting, twice the number seen in 1995.²

Urologic procedures are expected to increase by 35% in the United States as the population older than 65 years increases³; at present they make up 5% of all ambulatory procedures.⁴

Current office-based urologic procedures include flexible cystoscopy, transrectal prostate biopsy, urethral dilation, urethral meatotomy, vasectomy, varicocele repair, stone removal, circumcision, transurethral surgery of the bladder, and transurethral needle ablation of prostate lesions.¹

The growth of OBS can be attributed to advances in surgical techniques, associated with less postoperative pain coupled with the development of rapid-acting, safer anesthetics allowing for more complex procedures to be performed in an office-based facility. In addition, the economic demands to decrease health costs and patient preference for the nonhospital setting have contributed to its growth. The advantages of an office setting consist of a more personal, less intimidating environment for patients, ease of scheduling, lower

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costs, increased privacy, and decreased nosocomial infections.⁵ Patients' perception that procedures performed in the office setting are less invasive and, thus, safer, has also stimulated interest in OBS.⁶ A survey performed by Coyle and colleagues⁷ found that patients report an overwhelming satisfaction with OBA. Identified predictors of satisfaction were lack of pain and nausea, the ability to remember discharge instructions, and having no memory of the procedure. Identified predictors of dissatisfaction were anxiety, pain, vomiting, and inadequate depth of anesthesia.

OBA is not for every provider or patient, nor is OBS appropriate for every surgeon. Because of the remote location of the office setting, proper selection of patients and procedures is imperative. All types of anesthesia ranging from local, monitored anesthesia care (MAC), regional anesthesia, and general anesthesia (GA) can be performed in the office setting. The main priority of OBA is to minimize pain, postoperative nausea and vomiting (PONV), and postprocedure drowsiness, to ensure patient safety and satisfaction, and to provide a speedy discharge home. The disadvantage of office-based procedures lies with patient safety, owing to a lack of uniform oversight and regulation. In addition, the anesthesiologist may have to practice without backup, consultation, or clinical assistance.⁸ It is therefore imperative that the surgeon, anesthesiologist, and office staff ensure that the location where the OBA is being administered is safe.

Despite the rapid growth of OBS, it still remains unregulated in many states, and adherence to safety standards may not be uniform. This article focuses on the requirements for setting up a safe office-based practice, patient selection, and anesthetic management for OBS. The degree of evidence in literature in relation to office-based procedures and complications is not as extensive as that on ambulatory and day-case hospital-based surgery. Ambulatory surgery paradigms can be used for guidance in patient selection and management for OBS. Thus, mention is made herein of ambulatory and hospital-based day surgeries in the hope of extrapolating some of their management rationale to office-based procedures. It is safe to assume that patients who does not meet criteria for a procedure at an ambulatory facility should not be considered for OBS.

FACILITY CONSIDERATIONS AND ACCREDITATION

Despite the growing popularity of OBA and concerns about its safety, there is still relatively little oversight. Whereas ASCs are tightly regulated, OBS is limited in its regulatory oversight. Lack of

regulatory oversight may lead to OBS being performed in an environment with limited or outdated equipment, inadequate emergency resources, and insufficient policies. The skill level of the person providing anesthesia care may range from a board-certified anesthesiologist or certified registered nurse anesthetist (CRNA) to a surgeon with little or no anesthesia training. At present, only 25 states have issued guidelines to meet safety standards, 14 states require hospital transfer plans for emergency situations, and 9 states require reporting of complications.^{9–11} Eleven states now require accreditation through 1 of several agencies to evaluate the office-based practice setting.¹¹

The 3 major organizations for accreditation for OBS facilities are the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), The Accreditation Association for Ambulatory Healthcare (AAAHC), and the American Association for Accreditation of Ambulatory Surgery Facilities (AAAASF). These organizations differ in their requirements for reporting of adverse events and peer-review process, credentialing and privileging of practitioners without hospital privileges, and enforcement. Accreditation with these associations is voluntary in most states; however, most third-party payers will not reimburse the OBS facility for procedures performed in a nonaccredited office.¹⁰ The Federation of State Medical Boards issued guidelines in 2002 outlining recommended policies and procedures for physicians performing OBS. The American Medical Association (AMA) has also issued 10 core principles for establishing safety standards in offices, and these standards have been endorsed by state medical boards (**Box 1**).¹² In addition, several professional societies (American Society of Plastic Surgeons, American Society for Anesthetic Plastic Surgery, American College of Surgeons, American Society of Anesthesiologists [ASA]) have issued guidelines and recommendations for improving safety in ambulatory surgery or OBS/OBA.

The establishment, construction, accreditation, and operation of an OBS facility should be in accordance with the local, state, and federal laws.⁹ From an anesthesia standpoint the ASA has developed guidelines for OBA (**Table 1**).¹³ The ASA states that the anesthesiologist "must satisfactorily investigate areas taken for granted in the hospital or ambulatory surgical facility such as governance, organization, construction and equipment as well as policies and procedures including fire, safety, drugs, emergencies, staffing, training and unanticipated patient transfers." The anesthesiologist must adhere to these guidelines and communicate with the surgeon and staff the need to adhere to these safety guidelines.¹³

Box 1**American Medical Association (AMA) 10 core principles for establishing safety standards in offices**

- Patient informed consent should be obtained.
- Guidelines and regulation for OBS should be developed according to levels of anesthesia as defined by the ASA.
- Physicians should use the ASA patient selection classification in considering patient selection for surgery.
- Physicians should have proper qualifications such as board certification.
- Physicians should have hospital-admitting privileges or emergency transfer agreement.
- Facilities should be accredited.
- There should be a policy in place for adverse event reporting and peer review process.
- There should be a peer-review process for physician privileging, or a physician may show competence by maintaining core privileging at a licensed hospital or ASC.
- There should be at least 1 physician trained in ACLS/ATLS or PALS immediately available with appropriate equipment. BLS is mandatory for everyone else in direct patient contact.
- Those administering sedation/GA should be appropriately trained.

Abbreviations: ACLS, advanced cardiac life support; ATLS, advanced trauma life support; BLS, basic life support; GA, general anesthesia; OBS, office-based surgery; PALS, pediatric advanced life support.

Adapted from American Medical Association. Office based surgery core principles. Chicago: American Medical Association; 2003. Available at: <http://www.ama-assn.org/ama1/pub/upload/mm/370/obscoreprinciples.pdf>. Accessed March 1, 2013.

The facility should have a medical director who is ultimately responsible for the facility, the personnel, and observation of all local, state, and federal laws, codes, and regulations. A formal policy and procedure manual should be available to address issues such as provider qualifications, records, documents, quality improvement, professional liability, handling of controlled medications, and policy for clinical care issues. All health care providers should hold a valid license. The anesthesiologist should ensure that the local state and federal regulations concerning the use of controlled medications are followed. A fire safety plan should be in effect, and emergency evacuations rehearsed. The anesthesiologist should ensure the proper storage,

ventilation, and backup of operating-room gases. Anesthesiologists should also ensure that the equipment used is fully supported by the manufacturer or qualified service personnel and that backup electrical power is available, along with emergency lighting and protection against electric shocks or hazards. All elements of infection control should be properly practiced.^{13,14}

MONITORING AND EQUIPMENT

The ASA OBA guidelines state that there should be appropriate anesthesia equipment that is maintained and current, along with basic anesthesia monitoring. Monitoring is expected to be of hospital standard. **Box 2** describes the ASA statement on equipment for anesthesia in non-operating-room locations.¹⁵ **Box 3** describes the basics of anesthesia monitoring.¹⁶

PROCEDURE SUITABILITY

Clearly not all procedures are suited to the office. In general, procedures should be of short enough duration and complexity to allow patient recovery and discharge from the facility.¹³ The American Society of Plastic Surgeons has recommended that surgical procedures not exceed 6 hours and that all procedures be completed by 3 PM. Procedures more than 6 hours long may be associated with the development of hypothermia and increased risk for deep venous thrombosis.¹⁷ Surgical procedures involving major blood loss, intractable pain, or immobility severe enough to interfere with routine activities of daily living, as well as major intra-abdominal, intrathoracic, or intracranial surgeries, are unsuitable for the office setting.^{1,18}

PATIENT SAFETY IN OFFICE-BASED SURGERY

The statistics on morbidity and mortality in OBS are difficult to analyze and compare because of a lack of standard definitions and, thus, of adverse events. In addition, data that are available are conflicting.

Coldiron and colleagues¹⁹ reviewed OBS incidents in Florida over a 7-year period and found 31 reported deaths, 18 associated with cosmetic procedures and 13 associated with medically necessary procedures. Some of these procedures occurred with and some without a licensed anesthesia provider. Seventy-eight percent of the deaths reported occurred following the use of GA for the OBS procedure.

Vila and colleagues²⁰ reviewed all adverse events reported to the Florida Board of Medicine from 2000 to 2002, and found that the risk of death was 10 times higher in doctors' offices than in ASCs. The

Table 1
American Society of Anesthesiology (ASA) guidelines for office-based anesthesia

Administration and Facility	Clinical Care
Quality of Care The facility should have a medical director and governing body that establishes policy and is responsible for the facility and its staff Policy and procedures should be written and reviewed on an annual basis All applicable local, state, and federal regulations should be observed Health care providers should hold a valid license All operating-room personnel who provide clinical care should be qualified to do so The anesthesiologist should participate in ongoing quality improvement and risk-management activities The basic human rights of patients should be recognized Facility and Safety Facilities should comply with all federal, state, and local laws pertaining to fire, building construction and occupancy, accommodations for the disabled, occupational safety and health, and disposal of medical waste and hazardous waste Correct compliance with laws regarding controlled drugs	Patient and Procedure Selection The anesthesiologist should be satisfied that the procedure to be undertaken is within the scope of the facility and the health care practitioners The procedure should allow for the patient to be discharged that day Patients at too high risk should be referred to an appropriate facility Perioperative Care The anesthesiologist should adhere to the basic standards of preanesthesia care, basic anesthesia monitoring, and postanesthesia care, and guidelines for ambulatory anesthesia and surgery according to the ASA The anesthesiologist should be physically present during the intraoperative period and immediately available until discharge Patient discharge is the physician's responsibility and should be documented in the medical record Personnel with training in advanced resuscitative techniques (eg, ACLS, PALS) should be immediately available until all patients are discharged home Monitoring and Equipment See statement on non-operating-room anesthesia locations (see Table 3) See standards for basic anesthesia monitoring (see Table 4) Emergencies and Transfers All facility personnel should be appropriately trained in and regularly review the facility's written emergency protocols There should be written protocols for cardiopulmonary emergencies and other internal and external disasters such as fire The facility should have medications, equipment, and written protocols available to treat malignant hyperthermia when triggering agents are used The facility should have a written protocol in place for the transfer of patients to a prespecified alternative care facility when extended or emergency services are needed

Based on American Society of Anesthesiologists. Guidelines for office-based anesthesia. Last affirmed October 2009. Available at: <http://www.asahq.org/For-Members/Standards-Guidelines-and-Statements.aspx>. Accessed March 1, 2013; with permission. A copy of the full text can be obtained from ASA, 520 Northwest Highway, Park Ridge, Illinois 60068-2573.

investigators ascribed this to lack of observance to regulatory controls in doctors' offices.

Domino²¹ published results of a review of the ASA closed claims database to compare adverse events after OBA with anesthesia in the ASC setting. The severity of injury for office-based

claims was found to be greater than for ambulatory anesthesia claims. Sixty-four percent of the office-based claims concerned death, versus only 21% of ambulatory anesthesia claims. More than 46% of office-based claims were a result of adverse respiratory events in the recovery period that

Box 2**ASA statement on equipment for anesthesia in non–operating-room locations**

1. A reliable source of oxygen adequate for the length of the procedure and a backup supply of at least an E cylinder should be present.
2. An adequate source of suction should be present.
3. Scavenging system for scavenging waste anesthetic gases should be present.
4. The following should be present: (a) a self-inflating hand resuscitator bag; (b) adequate anesthesia drugs, supplies, and equipment for the intended anesthesia care; (c) standard ASA monitors; (d) a well-maintained anesthesia machine if inhalation anesthesia is to be administered.
5. Sufficient electrical outlets including an emergency power supply should be present. Also present should be an isolated electric power or electric circuits with ground fault circuit interrupters, if anesthetizing area is deemed a wet location.
6. There should be adequate illumination of the patient, anesthesia machine, and monitoring equipment. In addition, a form of battery-powered illumination should be immediately available.
7. There should be sufficient space to accommodate equipment and personnel and to allow access to the patient.
8. An emergency cart with a defibrillator, emergency drugs, and other equipment adequate to provide cardiopulmonary resuscitation should be present.
9. There should be adequate staff trained to support the anesthesiologist and a reliable means of 2-way communication to request assistance.
10. All applicable building and safety codes and facility standards should be observed.
11. Appropriate postanesthesia management should be provided. In addition to the anesthesiologist, adequate numbers of trained staff and appropriate equipment should be available to safely transport.

Based on American Society of Anesthesiologists. Guidelines for office-based anesthesia. Last affirmed October 2009. Available at: <http://www.asahq.org/For-Members/Standards-Guidelines-and-Statements.aspx>. Accessed March 1, 2013; with permission. A copy of the full text can be obtained from ASA, 520 Northwest Highway, Park Ridge, Illinois 60068-2573.

were judged to be preventable with the use of better monitoring.

Morelo and colleagues²² demonstrated a disturbing trend. During ASC procedures, 62% of injuries resulted in temporary nondisabling injuries and 21% in death. However, during office procedures 21% of injuries were temporary and non-disabling but 64% resulted in death. Moreover, 46% of injuries occurring in the office were considered preventable, as opposed to only 13% in an ASC. The adverse events that occurred in the office included respiratory (50%), cardiovascular (8%), equipment related (8%), drug related (25%), and blunt needle trauma.

Other studies, however, found that there is no difference in the rates of death and adverse events on comparing office-based procedures with ASC procedures.^{23,24}

PATIENT SELECTION FOR AMBULATORY SURGERY

Just as not all procedures are suitable for the office setting, neither are all patients well suited for OBS.

The staff surgeon should be aware of exclusions for OBA, screen the patient for suitability, and forward pertinent health information to the anesthesiologist for review before the day of surgery. Often the anesthesiologist meets the patients for the first time on the morning of surgery, so it is incumbent on the surgeon to ensure that the patient is appropriate for OBA and has undergone appropriate preoperating testing and evaluation. In general, the most suitable patients for OBS are those classified as ASA 1 and 2; however, patients of ASA 3 and 4 may be accepted if their disease states are compensated (**Box 4**).²⁵ Most recent recommendations and national surveys do not mention ASA grade as an exclusion criterion for office-based surgery.^{26,27} There is general consensus that patients of ASA 4 are at high risk for OBS.²⁸ However, this does not mean that OBS is contradicted, rather that the medical conditions degree of stabilization needs to be stringently assessed and the procedure in question thoroughly considered before accepting the patient for OBS.

One must take into consideration patients' chronic disease states and whether they are

Box 3
Standards for basic anesthesia monitoring

1. Qualified anesthesia personnel shall be present in the room throughout the conduct of all general anesthetics, regional anesthetics, and monitored anesthesia care.
2. During all anesthetics, the patient's oxygenation shall be continually evaluated.
 - During administration of GA using an anesthesia machine, the concentration of oxygen in the patient's breathing system shall be measured by an oxygen analyzer with a low oxygen concentration limit alarm in use.
 - During all anesthetics, pulse oximetry shall be used.
3. During all anesthetics, the patient's ventilation shall be continually evaluated.
 - Patients receiving GA shall have continual monitoring of expired carbon dioxide.
 - Alarms to detect and disconnect end-tidal CO₂ should be used.
 - During regional anesthesia (with no sedation) or local anesthesia (with no sedation), the adequacy of ventilation shall be evaluated by continual observation of qualitative clinical signs. During moderate or deep sedation, the adequacy of ventilation shall be evaluated by continual observation of qualitative clinical signs and monitoring for the presence of exhaled carbon dioxide.
4. During all anesthetics, the patient's circulation shall be continually evaluated.
 - Patients receiving anesthesia shall have the electrocardiogram continuously displayed from the beginning of anesthesia until preparing to leave the anesthetizing location.
 - Blood pressure and heart rate shall be determined every 5 minutes.
5. During all anesthetics, the patient's temperature shall be continually evaluated.
 - Patients receiving anesthesia shall have temperature monitored when clinically significant changes in body temperature are intended, anticipated, or suspected.

Based on American Society of Anesthesiologists. Standards for basic anesthesia monitoring. Last amended October 2010. Available at: <http://www.asahq.org/For-Members/Standards-Guidelines-and-Statements.aspx>. Accessed March 1, 2013; with permission. A copy of the full text can be obtained from ASA, 520 Northwest Highway, Park Ridge, Illinois 60068-2573.

Box 4
ASA physical class

- ASA Physical Status 1: A normal healthy patient
- ASA Physical Status 2: A patient with mild systemic disease
- ASA Physical Status 3: A patient with severe systemic disease
- ASA Physical Status 4: A patient with severe systemic disease that is a constant threat to life
- ASA Physical Status 5: A moribund patient who is not expected to survive without the operation
- ASA Physical Status 6: A declared brain-dead patient whose organs are being removed for donor purposes

Based on American Society of Anesthesiologists. ASA physical status classification system. Available at: <http://www.asahq.org/Home/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System>. Accessed March 1, 2013; with permission. A copy of the full text can be obtained from ASA, 520 Northwest Highway, Park Ridge, Illinois 60068-2573.

compensated and stabilized. Patients with uncontrolled medical problems or those severe enough to require hospitalization after surgery are unacceptable.

Urologic patients harbor the widest range of ages from infants to the elderly. Compared with the “average” patient undergoing surgery, however, they tend to be older and have more comorbid disease states. More than one-third of urologic patients have severe systemic disease, a higher prevalence than that seen in other specialties.²⁹ Exclusions to OBA are listed in **Box 5**.^{17,18,30} **Box 6** lists conditions that have been associated with adverse outcomes in ambulatory surgery.³¹

PREOPERATIVE EVALUATION

The preoperative evaluation should start with a thorough history and physical examination including health history, identification of comorbidities, social and family history, allergies, medications, review of systems, and anesthetic history. The physical examination should include

Box 5 Exclusions to OBA

- Unstable ASA 3 or 4
- Myocardial infarction (MI) in past 6 months
- Severe cardiomyopathy or congestive heart failure (CHF)
- Uncontrolled hypertension (HTN)
- Brittle diabetes
- Active multiple sclerosis
- Acute substance abuse
- History of malignant hyperthermia (MH) or strong family history of MH
- Severe morbid obesity (body mass index [BMI] >35 kg/m²)
- Morbid obesity (BMI>30 kg/m²) with poorly controlled comorbidities
- Severe obstructive sleep apnea or chronic obstructive pulmonary disease
- Pacemaker/automatic implantable cardioverter-defibrillator
- End-stage renal disease
- Sickle-cell anemia
- Dementia
- Patient on transplant list
- Recent stroke within 3 months
- Psychologically unstable
- Myasthenia gravis
- Lack of adult escort
- Difficult airway
- Acute illness
- Poorly compensated or incompletely evaluated systemic disease

Adapted from Refs.^{17,18,30}

vital signs, general appearance, height, weight, and examination of the cardiac and respiratory systems.¹⁷ An airway examination should be performed and documented to include the Mallampati score and assessment of state of dentition, mouth opening, and thyromental distance, and range of motion of the neck. The patient should be informed of nil-by-mouth instructions and anesthetic options (**Table 2**),³² and of the need to have a responsible adult available at the time of discharge.

Elderly Patients

Between 2005 and 2020 the elderly population is expected to increase by more than 53%,³³ which will result in the growth and demand for surgical

Box 6 Conditions shown to be associated with adverse outcomes in ambulatory surgery

- Congestive heart failure: 12% prolongation of postoperative stay
- Hypertension: 2-fold increase in risk of intraoperative cardiovascular events
- Asthma: 5-fold increase in the risk of postoperative respiratory events
- Smoking: 4-fold increase in the risk of postoperative respiratory events
- Obesity: 4-fold increase in the risk of intraoperative and postoperative respiratory events
- Gastroesophageal reflux: 8-fold increase in the risk of intubation-related adverse events

Adapted from Chung F, Mezei G. Adverse events in ambulatory anesthesia. *Can J Anaesth* 1999;46 (5 Pt 2):21; with permission.

therapies, some of which will undoubtedly be in the office setting.

Chronic medical conditions are more prevalent in the elderly. In patients 70 years or older, hypertension (HTN) is present in 45% to 50%, coronary artery disease (CAD) in 3% to 40%, diabetes in 12% to 15%, and chronic obstructive pulmonary disease (COPD) in 7% to 9%.³⁴ In a cohort study spanning over 5 years incorporating 1.2 million hospital-based outpatient surgeries, age greater than 85 years was one of the strongest predictors of hospital admission and death within 7 days of surgery.³⁵ Fleisher and colleagues²⁴ studied 564,267 patients older than 65 undergoing

Table 2
Guidelines for fasting before surgery

Food Material	Minimum Fasting Time (h)
Clear liquids (water, pulp-free juice, black coffee, carbonated beverages)	2
Breast milk	4
Infant formula/nonhuman milk	6
Light meal (toast)	6
Fried, fatty foods	8

Adapted from American Society of Anesthesiologists Task Force on Preoperative Fasting. Practice guidelines for preoperative fasting and the use of pharmacologic agents for the prevention of pulmonary aspiration: application to healthy patients undergoing elective procedures. *Anesthesiology* 1999;90:899; with permission.

hospital day-case surgery, ASC, and physician OBS. Age greater than 85 years, prior inpatient hospital admission within 6 months, and surgery at a physician's office identified those patients who were at greater risk of inpatient hospital admission or death within 7 days. The cardiovascular and respiratory response to anesthetics is altered in the elderly by age-induced alterations in pharmacodynamics and kinetics. Chung and Mezei³¹ found that the frequency of intraoperative adverse events increased linearly with increasing age, whereas the frequency of postoperative adverse events decreased.

However, elderly patients are at risk for cognitive dysfunction and confusion after surgery, and therefore may benefit from the secure, family environment of an office facility. Canet and colleagues³⁶ hypothesized that day surgery that minimizes the impact of surgery on daily activities and reduced separation from the home environment may be beneficial to the elderly. Improvements in anesthetic technique now allow patients to return to their baseline state as a result of newer medications with a shorter half-life and quicker elimination. This factor is particularly important in the elderly.

In conclusion, although perioperative complication rates are higher in the elderly, age itself is not a contraindication to OBS. However, elderly patients do require a more thorough preoperative evaluation and management of comorbidities.

Pediatrics

The minimum age in OBA for an otherwise healthy infant has not been established; however, it has been suggested to restrict selection of infants older than approximately 6 months and exclude ex-premature infants because of the risk of apnea. Obviously the personnel who care for children need to be Pediatric Advanced Life Support certified, and the facility needs to have age-appropriate equipment available.¹⁴

Obesity

Obesity is defined as an excess of body weight 20% greater than ideal body weight, or a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared, ie, kg/m²) of greater than 30. The obese population poses several issues with regard to ambulatory surgery and OBA. Hypertension, congestive heart failure, respiratory abnormalities, and diabetes are more common in the obese. The prevalence of cardiovascular disease in the obese population is 37%.³⁷ In addition, approximately 5% of morbidly obese patients have obstructive sleep apnea

(OSA).³⁸ Obese patients have been shown to have a significantly increased risk of intraoperative and postoperative respiratory events, including bronchospasm and desaturation caused by decreased functional residual capacity.³¹ Difficult intubation is more common in the obese population. Patients with a BMI greater than 35 or a BMI greater than 30 with other comorbidities are contraindicated for OBS.

Pulmonary

As mentioned earlier, asthma and COPD both increase the risk of perioperative complications. Patients should be well stabilized before considering OBA. Patients with asthma and COPD should be questioned on the severity of their symptoms, and medication use including steroids and any aggravating factors. Inhalers should be used as usual, and the patient instructed to bring them on the day of surgery. If the patient has worsening symptoms or poorly controlled COPD/asthma, the office is not an appropriate location for surgery.

In general, patients should stop smoking before surgery. Smoking increases airway reactivity, inhibits ciliary motility, causes poor wound healing, and increases the rate of complications after surgery.

The evaluating physician should inquire about signs associated with OSA such as snoring, chronic fatigue, and daytime somnolence. The prevalence of OSA is estimated to be 2% in women and 4% in men.³⁹

Serious long-term effects include an increase in sympathetic tone caused by chronic hypercarbia and hypoxia, which can lead to ischemic heart disease, hypertension, tachyarrhythmias, deterioration in cognitive function, pulmonary hypertension, cor pulmonale, congestive heart failure, cardiovascular accident/stroke, and sudden death.⁴⁰

Patients with OSA, owing to their airway anatomy, are at a higher risk of experiencing airway obstruction during sedation. The upper airway abnormalities associated with OSA can be the same as those that lead to difficult airway management and intubation. Snoring and OSA were found to be independent risk factors for difficult mask ventilation.⁴¹ Difficult intubation was found to occur 8 times more often in OSA patients than in control patients.⁴²

The prevalence of OSA is increasing, most likely as the prevalence of obesity and increased testing for OSA occurs. There is insufficient evidence in the literature to offer guidance as to which OSA patients can be cared for in the office.

However, the ASA has published practice guidelines for the perioperative management of patients with OSA. The task force stated that patients with documented OSA may be candidates for OBS if they do not require continuous positive airway pressure, will undergo a minimally invasive procedure, and have limited need for narcotic analgesia.³⁹

Neurologic

The evaluating physician should inquire about neurologic diseases such as previous stroke, multiple sclerosis, muscular disorders such as myasthenia gravis, and seizures. Antiseizure medications should be continued throughout the perioperative period. The patients' baseline functional and neurologic status should be documented. Patients with severe neurologic illnesses, uncontrolled seizures, or recent stroke are not candidates for OBA.

Renal

Chronic kidney disease can arise from numerous systemic diseases, HTN and diabetes being 2 common causes. Although patients with chronic kidney disease may be candidates for OBA, dialysis patients are not suitable for OBA.

Hepatic

Common causes of liver disease include cancer, alcohol abuse, infections such as hepatitis C, or autoimmune conditions. Patients with end-stage liver disease, ascites, coagulopathies, and encephalopathy are not candidates for OBA.

Diabetes

With regard to major surgery, diabetes has been associated with an increased risk of perioperative cardiac, respiratory, and infectious complications.⁴³ However, despite the increased risk of complications in diabetics undergoing major surgery, it is not an independent predictor of morbidity and mortality following day-case hospital and ASC surgery.⁴⁴ The comorbidities associated with diabetes such as difficult airway from stiff joint syndrome (decreased mobility of the atlantoaxial joint), silent myocardial infarction (MI), autonomic neuropathy, decreased ventricular compliance, gastroparesis, abnormal blood pressure, and decreased wound healing should be strongly considered before accepting a patient for OBA. In addition, the duration of the operative procedure, anesthesia, and the disrupted meal schedule, along with potential postoperative emesis, could lead to labile blood sugar levels. Intraoperative blood glucose monitoring should occur every 1 to 2 hours.⁴⁵ Only stable, well-controlled diabetics should be considered for OBA.

The history should include the type of diabetes (1 or 2), medications (insulin or oral medications), blood sugar control, and the presence of complications and associated disease states arising from diabetes. Patients should be given instructions on how to manage their diabetic medications before surgery (**Table 3**).⁴⁵

Cardiovascular Disease

A thorough cardiac history should be obtained. Patients with an MI within the previous 6 months, severe cardiomegaly, congestive heart failure

Table 3
Preoperative diabetic instructions

Medication	Day Before Surgery	Day of Surgery
Oral hypoglycemics	Continue oral hypoglycemic medications	Hold oral hypoglycemic medications
Insulin	Continue to take usual dose of insulin If prone to nocturnal or morning hypoglycemia, decrease nighttime dose by 20%–30%	Take 75%–100% morning dose of long-acting insulin (Lantus, Levemir) Take 50%–75% morning dose of intermediate-acting insulin (NPH, Lente, Ultralente) 70/30 mixed: replace with intermediate-acting insulin and take 50%–75% of morning insulin dose Short-acting insulin should not be taken
Insulin pump	Continue as usual	Continue basal rate

Adapted from Joshi GP, Chung F, Vann MA, et al, Society for Ambulatory Anesthesia. Society for Ambulatory Anesthesia consensus statement on perioperative blood glucose management in diabetic patients undergoing ambulatory surgery. *Anesth Analg* 2010;111(6):1382; with permission.

(CHF), or uncontrolled HTN, or patients who have a pacemaker or automatic implantable cardioverter-defibrillator are not candidates for OBA. All cardiac medications should be documented, including those with which the patient is advised to continue on the day of surgery.

The patients' functional class in metabolic equivalents (METs) should also be evaluated. The basal oxygen requirement by the body in its resting state is approximately 3.5 ml/O₂/kg/min in a 40-year-old 70-kg male. This quantity has been designated as 1 metabolic equivalent (MET). The ability to take care of oneself, activities of daily living, is equal to 1 MET. The ability to walk up a flight of stairs or walk up a hill is equal to 4 METs. The ability to perform at least 4 METs of activity indicates a good functional status, thus making the presence of severe underlying ischemic heart disease less likely.

Surgical risk in cardiac patients has been attributed to the type of surgery. High-risk surgery (aortic and major vascular procedures) has a greater than 5% risk of cardiac complications, intermediate-risk surgery (head and neck, orthopedic, intraperitoneal, and so forth) has a 1% to 5% risk of cardiac complications, and low-risk surgery (superficial procedures, biopsies, endoscopy) has a less than 1% risk of cardiac complications.⁴⁶ Most office-based procedures would be considered low-risk surgeries.

As per the ACC/AHA 2007 guidelines on the preoperative cardiac workup for noncardiac surgery, patients undergoing low-risk surgery, regardless of their functional capacity, need not undergo any further cardiac testing. However, if patients

show signs and symptoms of an active cardiac condition (**Table 4**), further evaluation is required before they undergo any procedure, even a low-risk one.⁴⁶ These patients clearly are unsuited to OBA.

Patients who have undergone coronary artery bypass grafting and are asymptomatic have been shown to have a low rate of adverse cardiac events.³⁴ Patients with cardiac stents pose another problem. If a patient has undergone revascularization of a coronary artery with a stent, serious consideration must be given as to whether antiplatelet (aspirin and clopidogrel) medication can be stopped. Premature discontinuation of antiplatelet medication can lead to an acute stent thrombosis, leading to Q-wave MI.⁴⁷ The period of time a patient must be on dual antiplatelet medication differs depending on the type of stent placed.

Patients undergoing balloon angioplasty need to wait 2 to 4 weeks to allow vessel healing before undergoing elective surgery. Those with bare-metal stents need to undergo 4 to 6 weeks of dual antiplatelet therapy to allow endothelialization of the stent. Patients with drug-eluting stents need to complete 12 months of dual antiplatelet therapy to allow for endothelialization of the stent before undergoing elective surgery. If clopidogrel must be stopped for surgery, aspirin should be continued during the perioperative period and clopidogrel restarted as soon as is safe.⁴⁷

In a survey by Mukerji and colleagues,⁴⁸ almost half of the urologists surveyed stated they would stop clopidogrel irrespective of its indication, and 40.7% never consulted a cardiologist before stopping clopidogrel.

Table 4 Active cardiac conditions (ACC/AHA)	
Unstable coronary syndromes	Unstable angina Acute MI: 7 d Recent MI: 7–30 d
Decompensated CHF	
Significant arrhythmias	High-grade AV block Mobitz 2 AV block Third-degree AV block Symptomatic ventricular arrhythmias Supraventricular arrhythmias including AF with HR >100 beats/min Symptomatic bradycardia New ventricular tachycardia
Severe valvular disease	Severe AS: mean pressure gradient >40 mm Hg, valve area <1 cm ² or symptomatic Symptomatic MS

Abbreviations: AF, atrial fibrillation; AS, aortic stenosis; AV, atrioventricular; CHF, congestive heart failure; HR, heart rate; MI, myocardial infarction; MS, mitral stenosis.

Adapted from Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. *Circulation* 2007;116(17):e424; with permission.

Patients with mild CHF should be carefully evaluated before deciding to treat them in the office setting. Patients with aortic stenosis are not candidates for OBA unless only for the most minor noninvasive procedure.

Gastrointestinal

The patient should be questioned on symptoms of acid reflux, dyspepsia, gastroparesis, and regurgitation. Signs and symptoms of reflux increase the risk of aspiration. Patients at high risk for aspiration (severe uncontrolled gastroesophageal reflux disease, gastroparesis, and so forth) are not candidates for OBA.

Prior Anesthetic History

A history of difficult intubation, PONV, poor pain control, and postoperative delirium or combativeness should be ascertained preoperatively. The patient should also be questioned regarding personal or family history of serious adverse anesthetic problems such as malignant hyperthermia or pseudo-cholinesterase deficiency.

Allergies and Social Habits

A history of alcohol intake, smoking, and illegal drug use should be obtained. These patients may be at risk for unexpected withdrawal symptoms following surgery, and have an increased tolerance to anesthetic agents and pain medications. Chronic drug or alcohol abusers are not candidates for OBA.

Medications

All medications and their dosages should be documented. Patients should be instructed on which medications need to be stopped before surgery and which medications need to be continued on the day of surgery (**Table 5**).⁴⁹ Management of patients on warfarin should be discussed with their primary physician or cardiologist.

PREOPERATIVE LABORATORY TESTING

At present there are no guidelines for preoperative testing in the OBS setting.¹ Often physicians order tests, as they wish to see what the patients' baseline values are. However, laboratory testing should be directed by findings on history and physical examination. Testing should not be ordered based on age. Although older patients are more likely to have abnormalities on testing, these tests are not as predictive of complications as is information gained from the history and physical.

In 2002 the ASA created a task force to develop a practice guideline for routine preoperative tests. The ASA encouraged that testing be based on information obtained from medical records, patient interview, physical examination, and type and invasiveness of planned procedure. Routine laboratory tests are not good screening devices and should not be used to screen for disease. Patients undergoing minimally invasive procedures may not need tests, and healthy patients do not need testing. A test should only be ordered if its result

Table 5
Medication instructions before surgery

Medications to be Taken on the Day of Surgery	Medications to be Held on the Day of Surgery	Herbals and Vitamins	Anticoagulants
b-Blockers	Oral hypoglycemic agents	Vitamin E 10–14 d before surgery	Aspirin: hold for 7 d
Asthma medications	Diuretics	Multivitamins 10–14 d before surgery	Clopidogrel: hold for 5 d (7 d if planning neuraxial block)
Antihypertensives (except ACE inhibitors and diuretics)	ACE inhibitors	Herbals 7 d before surgery	Dabigatran: hold for 3 d
Antiseizure medications	Angiotensin 2 antagonists		Prasugrel: hold for 7 d
Narcotic pain medications			Pletal: hold for 2 d (4 d if planning neuraxial block)
H2 and proton-pump inhibitors			NSAIDs: hold for 3 d (some NSAIDs need to be held longer, eg, Mobic 5 d, Feldene 11 d)
Cholesterol-lowering drugs.			
Cardiac medications			

Abbreviations: ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.

Data from Muluk V, Macpherson DS, Cohn SL, et al. Perioperative medication management. Available at: <http://www.uptodate.com/contents/perioperative-medication-management>. Accessed March 1, 2013.

will influence management. In general, test results within 6 months are acceptable if the patient’s medical history has not changed. If the patient’s condition has changed in the interim, laboratory tests within 2 weeks are more favored. Repetition of laboratory work should be avoided.⁵⁰

Pregnancy Testing

If a patient is found to be pregnant, an elective procedure will more than likely be canceled. A history and physical examination are inadequate to determine early pregnancy. Therefore, all premenopausal women of childbearing age who have not had tubal ligation or hysterectomy should have a preoperative pregnancy test.

Complete Blood Count

A complete blood count should be considered in patients who have a history of anemia, recent chemotherapy, or cardiovascular or renal disease.

Renal Function and Electrolytes

Blood urea nitrogen, creatinine, and electrolytes should be tested in patients with chronic liver disease, kidney disease, and diabetes, and also in patients who are on medications (diuretics, digoxin, angiotensin-converting enzyme inhibitors, and so forth) that may result in electrolyte or renal function abnormalities.

Blood Glucose

Blood glucose should be ordered for all patients with diabetes. It can also be considered in patients on chronic steroid use, as this may alter blood glucose homeostasis.

Prothrombin Time/Activated Partial Thromboplastin Time/International Normalized Ratio

If a patient is currently using anticoagulants such as warfarin or intravenous heparin, a prothrombin time/activated partial thromboplastin time (aPTT)/international normalized ratio (INR) should be drawn. Clopidogrel and enoxaparin do not cause any derangements in laboratory values. Neuraxial block for surgery (spinal/epidural or nerve block) is not an indication for aPTT and INR testing unless the patient was recently on anticoagulants.

Liver Function Tests

Liver function tests are generally ordered for patients with cirrhosis, alcohol abuse, or malnutrition. However, these conditions alone would preclude the patient from having OBA.

Chest Radiography

A thorough history and physical examination should direct the physician toward ordering a chest radiograph (CXR). The available evidence is not compelling enough to suggest that a CXR is indicated in asymptomatic patients older than 50 years who have no risk factors. Patients with significant risk factors for postoperative pulmonary complications, patients with active pulmonary disease, or those with abnormal lung sounds on physical examination may warrant a preoperative CXR irrespective of age; however, they are unlikely to be candidates for OBA. Patients with COPD, smokers, patients with stable cardiac disease, and patients with recent but resolved upper respiratory tract infections do not necessarily need a CXR.

Electrocardiography

When deciding whether to order an electrocardiogram (ECG), a history of cardiovascular or respiratory disease and type and invasiveness of surgery should be considered. ECG abnormalities may be more numerous in older patients. Patients older than 70 years have a 75% chance of having at least 1 abnormality. However, this may not be predictive of postoperative complications.⁵¹ Age alone should not be a criterion for ordering a preoperative ECG. According to the ACC/AHA 2007 guidelines, an ECG is not indicated for asymptomatic patients undergoing low-risk surgery or for patients who do not have any clinical risk factors who may be undergoing intermediate-risk surgery (**Box 7**).⁴⁶

TYPES OF ANESTHESIA

Sedation in the office traditionally has been provided by the surgeon or proceduralist. There is a general consensus that OBS procedures using traditional doses of local anesthesia (LA) with oral

Box 7
Clinical risk factors

- History of coronary artery disease
- History of compensated or prior heart failure
- History of cerebrovascular disease
- Chronic renal insufficiency
- Diabetes (insulin requiring)

Adapted from Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. Circulation 2007;116(17):e427; with permission.

sedation can sometimes be accomplished without a licensed anesthesia provider. Sedation administered by surgeons for procedures has been well documented in the literature. However, the fine line between conscious and deep sedation is ever evident. Published reports of patients receiving 300 mg fentanyl with 10 mg midazolam by a surgeon for office-based urologic procedures without the use of pulse oximetry or capnography may be abhorrent to an anesthesiologist, but was the practice in some offices.⁵² Complex procedures and patients with comorbidities probably warrant the presence of an anesthesiologist in an OBS setting.¹ There are many ways to administer anesthesia in the office-based setting, from LA only to minimal/moderate sedation, moderate to deep sedation, to GA. For certain procedures, regional or neuraxial anesthesia may be provided.

Local Anesthesia

The use of local infiltration of LA coupled with some degree of sedation is often enough for office-based procedures. LA provides excellent analgesia for the procedure and postoperative pain control. One advantage of local infiltration is the elimination of PONV as a potential complication.

Sedation

Sedation and analgesia comprise a continuum of states ranging from minimal sedation to GA. The ASA define the continuum of depth of sedation as shown in **Box 8**.⁵³ Because sedation is a continuum, it is not always possible to predict how a patient will respond. Those intending to produce a given level of sedation should be able to rescue patients whose level of sedation becomes deeper than intended. Rescue implies airway management, returning to the previous level of sedation and halting the procedure until the patient returns to the required depth of sedation.

Monitored Anesthesia Care

The term MAC is defined by the ASA as “a specific anesthesia service for a diagnostic or therapeutic procedure”; that is, sedation performed and supervised by a qualified anesthesia provider.⁵⁴ Many procedures performed in the office setting are amenable to MAC with or without supplemental LA administered by the surgeon. Performing MAC requires attentiveness to the entire procedure, as the depth of sedation needs to be tailored to the ever-changing level of surgical stimulation. Therefore, MAC is an anesthesiology service that uses the anesthesia providers’ expertise

Box 8

ASA definition of continuum of sedation

- **Analgesia/Minimal Sedation (Anxiolysis).** A drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.
- **Moderate Sedation/Analgesia (Conscious Sedation).** A drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained. Moderate sedation is often provided by non-anesthesia-trained doctors to sedate patients for procedures.
- **Deep Sedation/Analgesia.** A drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.
- **General Anesthesia.** A drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive-pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

Based on American Society of Anesthesiologists. Guidelines for office-based anesthesia. Last affirmed October 2009. Available at: <http://www.asahq.org/For-Members/Standards-Guidelines-and-Statements.aspx>. Accessed March 1, 2012; with permission. A copy of the full text can be obtained from ASA, 520 Northwest Highway, Park Ridge, Illinois 60068-2573.

to safely sedate a patient for a procedure, be it minimal, moderate, deep, or GA.⁵⁴

A surgeon, anesthesiologist, or patient may prefer MAC over GA because of perceived lighter doses of medications, quicker recovery, and improved safety. The ASA closed claims database shows that although there are fewer MAC than GA claims (121 vs 1519), 40% of the MAC claims were for death or permanent brain injury. Injuries from

MAC arose from oversedation leading to hypoxia as a result of respiratory depression.⁵⁵ This percentage is similar to that of GA. Deciding between MAC and GA depends on the surgery being performed, the comfort level of the surgeon and anesthesiologist, and patient preference.

General Anesthesia

GA may be necessary for the procedure or patient/surgeon preference. The anesthetic technique chosen should allow rapid recovery to baseline functions with little PONV, have a high safety profile, and be cost effective. Patients on chronic pain medications, those with anxiety disorders, or those who have tremors may not be able to lie still even with the use of MAC, in which case GA is warranted.

The advantages of GA include patient immobility and control of the airway. Disadvantages included the potential for coughing on emergence, PONV, higher doses of intravenous medications, a longer recovery period, and postoperative disorientation. Maintenance of anesthesia can be accomplished with volatile inhaled anesthetic, total intravenous anesthesia (TIVA), or a balanced anesthesia technique.

The compact size and portability of an intravenous infusion pump have made TIVA a popular choice for small offices because it minimizes the need for bulky anesthesia equipment, a scavenging system, and a malignant hyperthermia (MH) cart. However, if succinylcholine is to be used, MH supplies need to be available on site.¹⁴ TIVA usually comprises a propofol infusion with a benzodiazepine and an opioid. Often, short-acting narcotic infusions such as remifentanyl or alfentanil are used. A propofol infusion provides the advantage of being of quick onset and offset, rapidly titratable, and with little PONV. If inhalation anesthetics are to be used, recovery from an insoluble agent such as desflurane, which are more quickly eliminated when discontinued in comparison with more soluble agents such as sevoflurane or isoflurane, should be considered for maintenance of anesthesia.⁵⁶

General Anesthesia with Laryngeal Mask Airway Versus General Anesthesia with Endotracheal Tube

After the induction of GA, an endotracheal tube or a laryngeal mask airway (LMA) can be used to secure the airway.

The LMA will provide the ability to either mechanically ventilate the patient or allow the patient to breathe spontaneously. It does not adequately protect from the aspiration of gastric content. An

LMA causes less cardiovascular response than an endotracheal tube on insertion, and allows for a smoother emergence from anesthesia with less coughing. In a study by Higgins and colleagues⁵⁷ the use of an LMA for a general anesthetic was associated with a postoperative sore throat in 18% of patients, compared with a rate of 45% in patients who received an endotracheal tube.

An endotracheal tube ensures airway protection from aspiration of stomach contents and secretions. However, it is associated with a greater cardiovascular response during insertion and removal. In addition, because of airway reflexes it is more likely to produce a cough on emergence from anesthesia, leading to an increase in intra-abdominal pressure and possible suture-line failure. An endotracheal tube, for the most part, requires neuromuscular blockade for insertion, whereas an LMA does not.

Regional Anesthesia

Little has been written on the use of regional anesthesia, neuraxial blockade (spinal or epidural), or peripheral nerve block in the office setting. The advantages of regional anesthesia include the avoidance of GA and its potential side effects, a reduction in medications needed for anxiolysis or sedation, and adequate postoperative pain relief leading to reduced recovery time. Potential disadvantages include the risk of LA toxicity and potential nerve damage.

Placement of peripheral nerve blocks has trended toward the use of ultrasound guidance for block placement. This technique allows for direct visualization of the nervous and vascular structures, and continual observation of placement of the needle tip, allowing LA to be directly deposited in the correct areas and its spread observed. However, not all anesthesiologists are equipped with the skill set required to perform blocks under ultrasound guidance, and it may be technically difficult to perform blocks without an assistant. Therefore a single anesthesiologist working in an office setting may not be able to offer this type of anesthesia.

The selection of LA to be used depends on the desired duration of action and degree of motor blockage in addition to the onset time and safety profile. Frequently used LA includes lidocaine and mepivacaine, which are associated with a quick onset but a shorter duration of action. Bupivacaine is associated with a longer onset and duration of action, but has more severe cardiovascular side effects if injected intravascularly. Ropivacaine has a longer duration of action than

lidocaine or mepivacaine, with a safer side-effect profile than bupivacaine.

LA toxicity can occur with the intravascular administration of any local anesthetic. If amide LAs are being used, the practitioner should consider having 20% lipid infusion (Intralipid) available to reverse local anesthetic toxicity should intravascular injection occur.⁵⁸

POSTOPERATIVE NAUSEA AND VOMITING

One of the undesirable outcomes of anesthesia is PONV. Postoperatively these symptoms can lead to increased length of stay in the postanesthesia care unit (PACU), expanded nursing care, and decreased patient satisfaction. It has been shown that 0.1% to 0.2% of unanticipated postoperative hospital admissions occur as a result of severe PONV. In addition, adverse events such as aspiration, suture dehiscence, or even esophageal rupture have been attributed to PONV symptoms. Untreated PONV occurs in 20% to 30% of the general surgical population and in up to 70% to 80% of high-risk patients.⁵⁹

Risk factors for PONV can be divided into 3 groups: patient, anesthetic, and surgical.

Patient factors, which are considered to be independent predictors of PONV, include female gender, nonsmoking status, and a history of PONV or motion sickness. Use of volatile anesthetics, nitrous oxide, and opioids has all been shown to be associated with an increased incidence of PONV. Surgical risk factors include the type of surgery being performed as well as the duration of surgery. Gynecologic, abdominal, and laparoscopic surgery has the highest incidence of PONV, and it has been shown that each 30-minute increase in the duration of surgery increases the risk of PONV by 60%.⁵⁹

The onset of PONV symptoms can be decreased by reducing or avoiding the risk factors previously stated and the administration of prophylactic medications. One method of reduction of baseline factors can be achieved by changing the type of anesthesia or anesthetic agents used. The risk of PONV is 9 times less in those receiving regional anesthesia than in those receiving GA; thus, if feasible, regional anesthesia should be used instead of GA. Because volatile anesthetics and nitrous oxide have been shown to increase the occurrence of PONV, the use of an alternative technique, TIVA with propofol, should be considered. The minimization of intraoperative and postoperative opioids, minimization (<2.5 mg) or avoidance of neostigmine, and adequate hydration have also been shown to decrease the incidence of PONV.⁵⁹

Universal PONV prophylaxis is not cost effective. Apfel and colleagues⁶⁰ devised risk stratification for administration of antiemetic prophylaxis based on a risk score (Table 6). Risk factors included female gender, prior history of PONV or motion sickness, nonsmoking, and postoperative opioids. The greater the number of risk factors present, the higher the incidence of PONV. Low-risk patients with a risk score of 0 to 1 should receive no prophylaxis. Moderate-risk patients with a risk score of 2 should receive monotherapy prophylaxis. High-risk patients with a risk score of 3 to 4 should receive combination therapy with 2 to 3 agents from different classes, and a TIVA performed as the primary anesthetic.⁵⁹

ANTIEMETIC OPTIONS FOR PROPHYLAXIS OF PONV

Gan and colleagues⁵⁹ and The American Society for Ambulatory Anesthesia have issued guidelines for the management of PONV (Fig. 1). There are many different options of antiemetic prophylaxis (Table 7).⁶¹ Classes include serotonin (5-HT₃) antagonists, butyrophenones, phenothiazines, anticholinergics, steroids, antihistamines, and some other alternative antiemetics such as propofol. The authors generally use dexamethasone at the beginning of the case coupled with a 5-HT₃ antagonist at the end of the procedure as prophylaxis. When no prophylactic medication has been given perioperatively, a 5-HT₃ antagonist is the recommended first line treatment option. A scopolamine patch can also be placed preoperatively, best placed on the evening before or at least 4 hours before surgery.⁶² Metoclopramide has been proved to be ineffective against PONV.⁵⁹ Aprepitant is a new NK1 receptor

Table 6
Simplified risk score for prediction of PONV (Apfel score)

Number of Risks Present	Risk of PONV (%)
0	10
1	21
2	39
3	61
4	79

Risk factors include female gender, history of PONV or motion sickness, opioid use and nonsmoker.

Adapted from Apfel CC, Laara E, Koivuranta M, et al. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between 2 centers. *Anesthesiology* 1999;91(3):697; with permission.

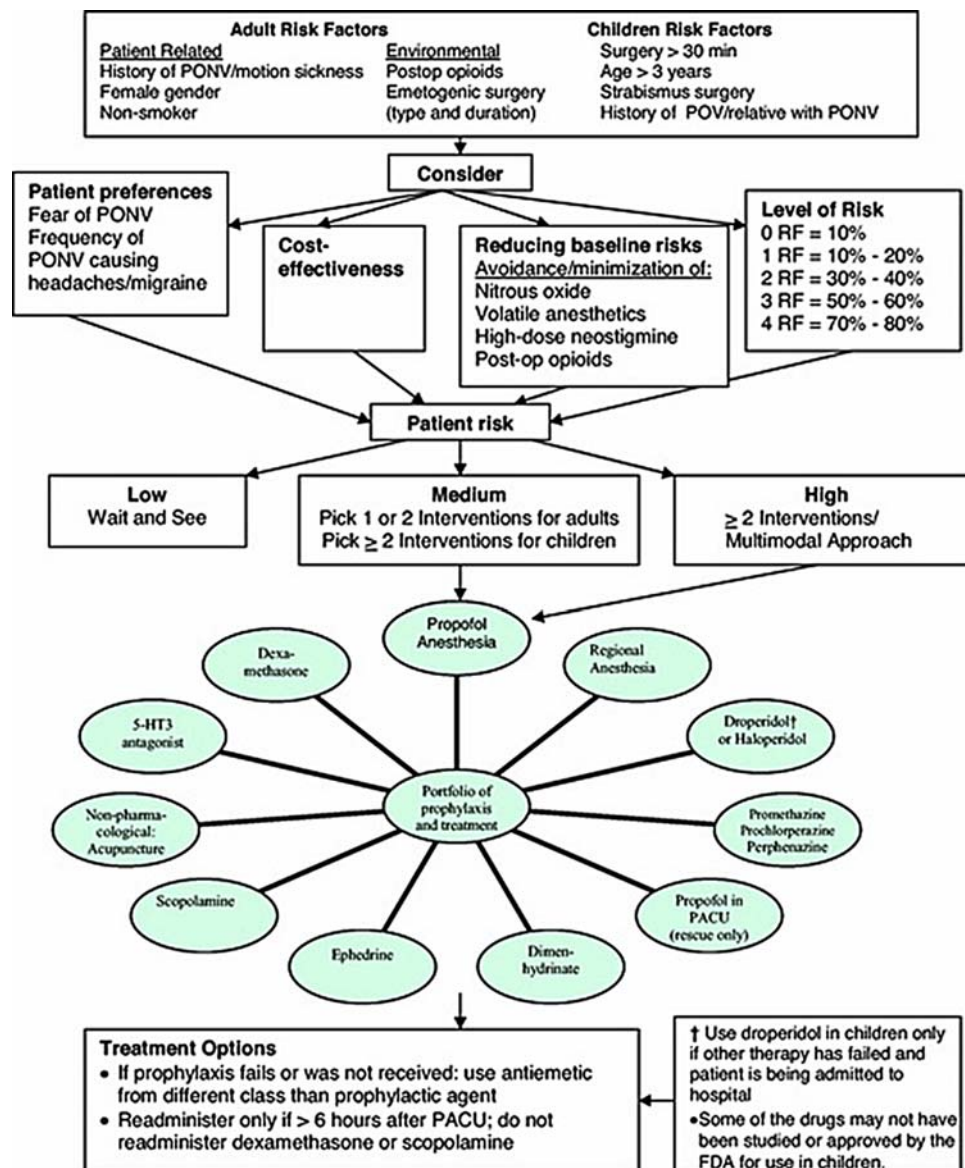


Fig. 1. Algorithm for management of postoperative nausea and vomiting (PONV). (From Gan TJ, Meyer TA, Apfel CC, et al. Society for ambulatory anesthesia guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 2007;105(6):1619; with permission.)

antagonist antiemetic used for the prevention of chemotherapy-induced nausea and vomiting.

RESCUE THERAPY

If the initial agent is ineffective, a second medication from a different class should be administered. Droperidol and 5-HT₃ antagonists may be repeated every 6 hours. Repeating the medication given for PONV prophylaxis within 6 hours postoperatively does not provide any additional benefit. Readministration of dexamethasone or scopolamine is not recommended because it is not

effective. Propofol, in small doses, is a powerful antiemetic. It may be used as a rescue antiemetic when all other therapies have failed, but because of potential complications must only be administered by trained anesthesia personnel in a monitored setting (ie, PACU).⁵⁹

OPTIONS FOR POSTOPERATIVE PAIN MANAGEMENT

Uncontrolled pain and opioid-related side effects are major contributors to delayed recovery and discharge after surgery. A multimodal analgesia

Table 7
Antiemetics

Drug Class	Dose	Timing	Side Effects
5-HT ₃ Antagonists			
Ondansetron	4 mg IV	End of surgery	Increased LFTs
Granisetron	0.35–1.5 mg IV		Headache
Dolasetron	12.5 mg IV		Constipation
Tropisetron	2 mg IV		
Antihistamine			
Dimenhydrinate	1 mg/kg IV	Unknown	Sedation
Butyrophenones			
Droperidol	0.625–1.25 mg IV	End of surgery	Drowsiness
Halopridol	0.5–2 mg IV		Agitation
			Extrapyramidal side effects
			QT prolongation
Phenothiazines			
Promethazine	6.25–25 mg IV	End of surgery	Agitation
Prochlorperazine	5–10 mg IV		Extrapyramidal side effects
			Drowsiness
Steroid			
Dexamethasone	4–5 mg IV	At induction	Unknown
			No adverse events with single administration
Other			
Propofol	20 mg IV	In PACU by anesthesiologist	Respiratory
Other			
Scopolamine	Transdermal Patch	4 h before end of anesthesia	Sedation
			Confusion
			Dry mouth

Abbreviations: IV, intravenous; LFTs, liver function tests; PACU, postanesthesia care unit.

Adapted from Galway U. Ambulatory anesthesia. In: Urman RD, Ehrenfeld JM, editors. Pocket anesthesia. 2nd edition. Philadelphia: Lippincott Williams & Wilkins; 2009; with permission.

Table 8
Intravenous analgesics

Drug Class	IV Dose and Interval	Side Effects
NSAIDs		
Ketorolac	Ketorolac 30 mg q 4–6 h	Renal failure Peptic ulcer Platelet dysfunction
Opioids		
Fentanyl	Fentanyl 25–100 mg q 30–60 min	Sedation
Morphine	Morphine 1–5 mg q 2–4 h	Respiratory depression
Hydromorphone	Hydromorphone 0.2–0.6 mg q 2–3 h	Pruritus
Meperidine	Meperidine 25–100 mg q 1–2 h	PONV
		Constipation
		Dysphoria
Acetaminophen	1000 mg IV q 6 h	Hepatic failure with overdose
Mixed Agonists/Antagonists		
Butorphanol	Butorphanol 20 mg/kg q 3–4 h	Sedation with no significant respiratory depression
Nalbuphine	Nalbuphine 0.25 mg/kg q 3–6 h	

Adapted from Galway U. Ambulatory anesthesia. In: Urman RD, Ehrenfeld JM, editors. Pocket anesthesia. 2nd edition. Philadelphia: Lippincott Williams & Wilkins; 2009; with permission.

Table 9 Oral analgesics		
Drug Class	Dose and Interval	Side Effects
NSAIDs		
Ibuprofen	Ibuprofen 400–800 mg q 6–8 h	Renal failure
Naproxen	Naproxen 500 mg q 8 h	Peptic ulcer
Ketorolac	Ketorolac 10–20 mg q 4–6 h	Platelet dysfunction
Diclofenac	Diclofenac 50 mg q 8 h	
Cyclooxygenase-2 Inhibitors		
Celecoxib (Celebrex)	200–400 mg q 12 h	Hypertension Edema Heart failure
Opioids		
Oxycodone	Oxycodone 5–10 mg q 4–6 h	Sedation
Morphine	Morphine 10–30 mg q 3–4 h	Respiratory depression
Hydrocodone	Hydrocodone 5–10 mg q 4–6 h	Pruritus
Codeine	Codeine 15–60 mg q 4–6 h	Nausea
Meperidine	Meperidine 50–150 mg q 3–4 h	Constipation
Hydromorphone	Hydromorphone 2–4 mg q 4–6 h	Dysphoria
Tramadol	Tramadol 50–100 mg q 4–6 h	
Opioid/Nonopioid Combinations		
Acetaminophen/propoxyphene napsylate (Darvocet)	1–2 tablets q 4–6 h	Sedation Respiratory depression Pruritus
Acetaminophen/oxycodone (Percocet)		Nausea
Acetaminophen/codeine (Tylenol) with codeine		Constipation
Acetaminophen/hydrocodone (Vicodin)		Dysphoria
Aspirin/oxycodone (Percodan)		Hepatic failure with overdose
Acetaminophen	Acetaminophen 650–1000 mg q 4–6 h	Hepatic failure with overdose

Adapted from Galway U. Ambulatory anesthesia. In: Urman RD, Ehrenfeld JM, editors. Pocket anesthesia. 2nd edition. Philadelphia: Lippincott Williams & Wilkins; 2009; with permission.

Table 10 Alternative analgesics	
Local anesthetics	Neuraxial anesthesia Regional nerve block Local infiltration Subcutaneous catheter placement with continuous infusions of dilute local anesthetic
Intranasal	Fentanyl Meperidine Butorphanol
Intramuscular	Meperidine Morphine Hydromorphone
Transdermal	Fentanyl patch
Others	Transcutaneous electrical nerve stimulation Acupuncture Acupressure

Adapted from Galway U. Ambulatory anesthesia. In: Urman RD, Ehrenfeld JM, editors. Pocket anesthesia. 2nd edition. Philadelphia: Lippincott Williams & Wilkins; 2009; with permission.

or balanced technique refers to the use of more than 1 medication or class of analgesic medication combined with regional anesthesia to produce adequate analgesia. This technique should be used whenever possible to limit the potential side effects associated with opioid use. Adjunct medications such as nonsteroidal anti-inflammatories and cyclooxygenase-2 inhibitors have been shown to reduce opioid requirements and improve pain control after surgery. Options for intravenous, oral, or alternative pain medications are listed in [Tables 8–10](#).⁶¹

DISCHARGE CRITERIA AND FAST-TRACKING

Recovery from anesthesia is generally divided into 2 phases. Phase 1 lasts from discontinuation of anesthetic until patients awaken and regain their vital protective airway reflexes. Phase 1 generally begins in the operating room and continues in a PACU.

The authors use a postanesthesia recovery score, such as the Aldrete score ([Table 11](#)), to evaluate initial patient recovery.⁶³ The patient

Table 11
The modified Aldrete scoring system for determining patient readiness for discharge from the postanesthesia care unit

Discharge Criteria from PACU	Score
Activity: able to move voluntarily or on command	
Four extremities	2
Two extremities	1
Zero extremities	0
Respiration	
Able to deep breathe and cough freely	2
Dyspnea, shallow or limited breathing	1
Apneic	0
Circulation	
Blood pressure ± 20 mm of preanesthetic level	2
Blood pressure ± 20 –50 mm preanesthesia level	1
Blood pressure ± 50 mm of preanesthesia level	0
Consciousness	
Fully awake	2
Arousable on calling	1
Not responding	0
O ₂ saturation	
Able to maintain O ₂ saturation >92% on room air	2
Needs O ₂ inhalation to maintain O ₂ saturation >90%	1
O ₂ saturation <90% even with O ₂ supplementation	0

A score ≥ 9 is required for discharge.

Adapted from Aldrete JA. The post-anesthesia recovery score revisited. J Clin Anesth 1995;7(1):89; with permission.

must reach a score of 9 before being considered as being in phase 2. Phase 2 is the intensive observation and stabilization of the patient until fit for discharge home. This phase generally occurs in the day-surgery step-down unit, which is not likely to be present in an OBS facility.

Home-readiness can be evaluated by a modified postanesthetic discharge scoring system, with a score of 9 required for discharge (Table 12).⁶⁴ Oral intake is not necessary before discharge. Voiding is also unnecessary unless the patient received neuraxial anesthesia or has undergone gynecologic, hernia, anorectal, or genital surgery.^{64,65}

Table 12
Modified postanesthetic discharge scoring system

Discharge Criteria	Score
Vital Signs	
Within 20% of preoperative value	2
20%–40% of preoperative value	1
40% of preoperative value	0
Ambulation	
Steady gait/no dizziness	2
With assistance	1
None/dizziness	0
Nausea/vomiting	
Minimal	2
Moderate	1
Severe	0
Pain	
Minimal	2
Moderate	1
Severe	0
Surgical bleeding	
Minimal	2
Moderate	1
Severe	0

A score ≥ 9 is required for discharge.

Adapted from Chung F, Chan VW, Ong D. A postanesthetic discharge scoring system for home readiness after ambulatory surgery. J Clin Anesth 1995;7(6):501; with permission.

For patients who have received spinal/epidural anesthesia, resolution of the sensory and motor block must occur and be documented before discharge. Patients who have received an extremity peripheral nerve block may be discharged before full regression of motor and sensory block, with instructions to protect the limb.⁶⁶

Fast-tracking refers to bypassing the PACU or phase 1 and going straight to phase 2 from the operating room (Aldrete score of 10 in the operating room; see Table 11). These patients can be discharged home earlier without any increase in complications or side effects. White and Song⁶⁷ proposed fast-tracking criteria that take into consideration pain and emetic symptoms (Table 13).

The office-based practice depends on a rapid transition from the initial stages of recovery to formal discharge in a short period of time, with as little postanesthetic cognitive and psychomotor impairment as possible. In general, fast-tracking applies to most patients who undergo OBA, owing

Table 13
White's scoring system to determine whether outpatients can be transferred directly from the operating room to the step-down (phase II) unit (fast-tracked)

Discharge Criteria	Score
Level of consciousness	
Awake and oriented	2
Arousable with minimal stimulation	1
Responsive only to tactile stimulation	0
Physical activity	
Able to move all extremities on command	2
Some weakness in movement of extremities	1
Unable to voluntarily move extremities	0
Hemodynamic stability	
Blood pressure <15% of baseline mean arterial pressure (MAP) value	2
Blood pressure 15%–30% of baseline MAP value	1
Blood pressure >30% below baseline MAP value	0
Respiratory stability	
Able to breathe deeply	2
Tachypnea with good cough	1
Dyspneic with weak cough	0
Oxygen saturation status	
Maintains value >90% on room air	2
Requires supplemental oxygen (nasal prongs)	1
Saturation <90% with supplemental oxygen	0
Postoperative pain assessment	
None, or mild discomfort	2
Moderate to severe pain controlled with IV analgesics	1
Persistent severe pain	0
Postoperative emetic symptoms	
None, or mild nausea with no active vomiting	2
Transient vomiting or retching	1
Persistent moderate to severe nausea and vomiting	0

Total possible score is 14. A minimal score of 12 (with no score <1 in any individual category) would be required for a patient to be fast-tracked (ie, bypass the postanesthesia care unit) after general anesthesia.

Adapted from White PF, Song D. New criteria for fast-tracking after outpatient anesthesia: a comparison with the modified Aldrete's scoring system. *Anesth Analg* 1999;88:1071; with permission.

to the administration of anesthesia with a quick recovery and few side effects.

The same standards for hospital-based or ASC recovery and discharge apply to the OBS setting. A formal recovery area with recovery-room orders and postoperative record should be the standard. A nurse trained in recovery-room procedures should be available to provide care in a properly equipped location until the patient is discharged. The anesthesiologist or equivalent should remain on the premises until the patient meets discharge criteria. The ASA recommend standard monitoring for all patients in the recovery room regardless of the type of anesthesia.⁶⁸ The patient should receive written instructions that include the management of pain, postoperative complications, and routine and emergency follow-up. Other than procedures occurring under LA only, the patient should be discharged into the care of a responsible adult. Personnel trained in basic life support/advanced cardiac life support should be present until the last patient leaves the facility.

SUMMARY

Advances in surgical techniques, coupled with the development of faster-acting, safer anesthetics, allow for more invasive procedures to be performed in an office setting. In addition, economic demands to decrease health costs and patients' preference for a nonhospital setting have contributed to the growth of OBS, and will continue to fuel its growth in the future.

Regulation of OBS is suboptimal at present, and monitoring of safety is questionable. It is imperative that we continue to strive to hold the OBS centers to the same standards as in ambulatory and hospital settings with regard to patient safety. We must continue to inform and train anesthesiologists in this field such that they can be an integral part of the continuing growth and safety of OBS.

Anesthesia for OBS should be such that the patient recovers quickly with few side effects or pain, and has a timely discharge. Options for this include GA with TIVA with consideration of LMA instead of endotracheal tube, MAC sedation, regional anesthesia, neuraxial anesthesia with the use of short-acting agents, local infiltration by the surgeon with light sedation, and minimization of PONV and pain.

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Office-Based Management of Impotence and Peyronie's Disease

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KEYWORDS

• Erectile dysfunction • Impotence • Peyronie's disease • Office-based

KEY POINTS

- Even though increased basic science research into the pathophysiology of Peyronie's disease has brought about new insights into the potential cause and treatment options, a reliable and effective nonsurgical therapy still eludes practicing urologists.
- A key to elucidating the beneficial effects of various medical therapies lies in the standardized evaluation of patients with Peyronie's disease across various studies, allowing these proposed benefits to be confirmed and applied to all populations.
- Some combination of intralesional injection with traction therapy may provide a synergy between the chemical effects of the drugs and the mechanical effects of traction.
- Currently available nonsurgical treatments can be used safely and may result in some reduction of deformity with improved sexual function.

INTRODUCTION

In the expanding field of men's health, much recent attention has been directed toward sexual health, an integral part of overall male wellness. Erectile dysfunction (ED) or impotence is a multifactorial disorder that continues to be an evolving public health concern. With the introduction of readily accessible, effective, and generally safe oral medications, men are now turning to primary care physicians and midlevel providers to manage conditions of sexual dysfunction and are often offered therapy with inadequate or no evaluation. Typically, the failure or poor efficacy of first-line treatments often leads to urology referral. Other reasons for specialty referral may be trauma, uncertainty of diagnoses, or simply the wish of patients or providers to better understand the cause of the ED. This article focuses on the office-based work-up, diagnosis, and management of 2 important and variable conditions in male sexual dysfunction, ED and Peyronie's disease (PD).

BACKGROUND

ED is the consistent or recurrent inability to attain or maintain penile erection adequate for sexual intercourse.¹ ED is a common male disability associated with aging that significantly impacts quality of life and interpersonal well-being.²⁻⁷ A 3-month minimum duration is generally accepted for establishment of the diagnosis, although in certain cases of trauma or surgically induced ED, a 3-month minimum may not be necessary. Although objective testing or partner reports help support a diagnosis of ED, these cannot replace patients' self-reports in classifying the dysfunction or establishing the diagnosis.⁸

Early landmark studies, such as the Massachusetts Male Aging Study (MMAS) and the National Health and Social Life Survey, used single-item scales, which assessed erection difficulties over several months or in the past year.^{9,10} In the MMAS, a community-based survey of men between 40 and 70 years of age, 52% of all

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respondents reported some degree of ED: 17% mild, 25% moderate, and 10% complete.¹¹ The MMAS showed that the incidence increased with patient age, with an incidence of 12.4 for men aged 40 to 49 years, 29.8 for men aged 50 to 59 years, and 46.4 for men aged 60 to 69 years. Other studies from the 1990s estimated that half of men older than 40 years had ED.² The degree of bother associated with ED has been shown to be inversely related to aging. Men older than 70 years typically report a lesser degree of bother as compared with their younger counterparts. Distress and treatment seeking related to ED is found to be higher in younger and middle-aged men.^{12–14} Recent investigation of the causes and risk factors for ED has revealed an association between ED, benign prostatic hyperplasia, and lower urinary tract symptoms.^{15–18}

The prevalence and incidence of ED are highly correlated with the presence of specific risk factors and comorbidities, suggesting that ED may be an early marker for cardiovascular and other disease states.^{19–24} In fact, the symptoms of ED can predate the clinical diagnosis of associated vascular disease by up to 3 years. Cardiovascular comorbidities (such as hypertension and hypercholesterolemia), diabetes mellitus, and metabolic syndrome have been associated with ED in multiple cross-sectional and longitudinal studies.^{13,19,25,26} Recent studies in hypogonadal men with testosterone deficiency syndrome (TDS) have demonstrated the positive benefits of normalizing testosterone in men with sexual problems. The development of new treatment options has provided men with TDS with improved and effective methods for hormone replacement, including topical gels and time-released pellets. In addition, the introduction of oral phosphodiesterase-5 (PDE-5) inhibitors resulted in patients presenting to their physicians in increasing numbers for evaluation and treatment earlier.²⁷ It is estimated that 25 to 30 million men worldwide are taking PDE-5 inhibitors and that an additional 50 million or more are potential candidates for treatment.^{12,23,28}

IDENTIFICATION OF RISK FACTORS/COMORBIDITIES

The Second International Consultation on Sexual Dysfunction identified specific risk factors for ED.¹ The factors have been well studied and include cigarette smoking; diabetes mellitus; hormonal disorders; cardiovascular disease; hypertension; chronic renal failure; lower urinary tract symptoms; poor overall health; chronic neurologic diseases; spinal cord injury; surgery and radiotherapy for prostate cancer; psychiatric

conditions, including anxiety disorders and depression; medications; and recreational drugs. Recognition of screening for these important risk factors is vital in the proper clinical evaluation of ED. The International Society of Sexual Medicine (ISSM) categorizes ED into 3 main groups: (1) psychogenic; (2) organic; and (3) mixed (organic and psychogenic), the most common type.⁴ The first goal of the in-office evaluation is the identification of risk factors and classification of patients with ED into one of these 3 groups.

PSYCHOGENIC ED

Identifying the proper psychogenic component to ED helps in guiding the treatment plan. According to the ISSM's classification, psychogenic ED may be generalized or situational. Generalized psychogenic ED usually relates to a primary lack of sexual arousability, aging-related decline in arousability, personality characteristics, or a chronic disorder of sexual intimacy. It is usually not associated with a particular sexual partner, situation, or performance concern.^{8,29} The situational type of psychogenic ED is associated with a specific partner, performance concerns, or adjustment-related issues. Partner-related issues may include lack of arousability in a specific relationship, sexual object preference, and partner conflict or threat.³⁰ Performance-related issues can be associated with situational performance anxiety or with other sexual dysfunctions, such as premature ejaculation or disorders of orgasm.^{31,32} Adjustment-related issues include major life stress, such as significant illness and death of a partner.³² Concomitant depressive and anxiety disorders have been associated with ED. The treatment of these disorders often reduces the severity and may treat the ED, although it is important to recognize the potential sexual side effects of the various antidepressant agents.^{33–36} In certain patients, psychological counseling and behavioral therapy may be helpful in addition to medical treatments for ED.^{32,36–39}

ORGANIC ED

If the clinical evaluation suggests an organic cause, the ISSM's classification system identifies the following major subgroups: neurogenic, hormonal, arterial, cavernosal (venogenic), and drug induced.¹ In addition, various disease states are identified as potential causes of ED through unclear mechanisms.

Lifestyle factors, including smoking, obesity, and lack of exercise, have been shown to be significant predictors of organic ED.^{25,40,41} In a

randomized, prospective, controlled trial, intensive lifestyle modification improved erectile function and associated cardiovascular and inflammatory markers.²⁶

NEUROLOGIC

There are many neurologic conditions that can affect ED. In theory, any neurologic condition involving autonomic innervation of the corpora cavernosa may impact the ability to produce a normal erection. Polyneuropathy, which commonly involves autonomic dysfunction, has been shown to be a source of ED.⁴² A study by Vardi and colleagues⁴³ reported a 38% coincidence of polyneuropathy and ED in patients with diabetes and a 10% coincidence of the two in patients without diabetes. Male sexual dysfunction is also seen in other neurologic conditions, such as Parkinson disease, dementia, multiple sclerosis, and other neurodegenerative diseases.^{39,44–48} In these disorders, the cause of ED is thought to result from a complex relationship of altered erectile nerve function, generalized sensorimotor impairment, cognitive decline, illness-related stress, and decreased interpersonal interaction.^{44–46} Epilepsy has also been linked to neurologic ED as well as reduced sexual interest/libido and desire.⁴⁴ Multiple sclerosis has been found to have an incidence of ED in the range of 40% to 80%. In these cases, ED typically presents 5 to 10 years after the onset of progressive neurologic symptoms.⁴⁷ Stroke, one of the most common neurologic conditions worldwide, is associated with ED in 50% to 65% of patients. Patients who have had a stroke also report a loss of sexual interest and desire and ejaculatory dysfunction.^{48–50} Patients with various spinal cord injuries may have significant problems with ED and other related sexual dysfunction. These problems tend to be most bothersome in regard to future quality of life.^{39,44}

ENDOCRINE

Erections, sexual behavior, desire, and interest can be affected by abnormalities of endocrine function.^{51,52} Gonadal function in men may deteriorate in a progressive way as part of the normal aging process.^{53,54} A low testosterone level is the most widely recognized and investigated hormonal alteration associated with the aging process, and hypogonadotropic hypogonadism may be an associated finding in ED. There is increasing evidence that androgens are fundamental, not just for sexual behavior and desire but also for various physiologic and signaling pathways regulating erection as well as for preserving bone density and muscle

mass.⁵⁵ Although hypogonadism is the most common endocrine cause of ED, thyroid disease, other pituitary disorders, adrenal disease, and hyperprolactinemia may all be associated with ED. The production of several hormones, including dehydroepiandrosterone, thyroxine, melatonin, prolactin, and growth hormone, is also affected by age and may have implications in erectile function.^{52,56} In significantly hypogonadal men, androgen-replacement therapy has been shown to improve nocturnal penile tumescence testing as well as erotic stimulus-evoked erections.^{57–59} The exact role of androgens in normal and abnormal erectile function remains an area of investigation.

VASCULAR

Vascular disease is the most common cause of organic ED.⁶⁰ Vasculogenic ED accounts for approximately 60% to 80% of all cases and can be classified into 3 subtypes: arterial, venoocclusive, or mixed vascular insufficiency.⁶⁰ ED shares a common pathophysiology with other vascular disease states, such as heart disease, stroke, and peripheral vascular disease. The accepted pathophysiologic mechanism is thought to be a reduction of inflow into the cavernosal arteries and venoocclusive dysfunction secondary to atherosclerotic occlusive disease.⁶⁰ The concept of ED as a marker of other underlying vascular disease is, in part, based on the finding that penile vascular disease shares a causal pathway with other vascular disease states, such as cerebrovascular disease, myocardial infarction, coronary artery disease, hypertension, hyperlipidemia, and peripheral vascular disease.⁶¹ In studies, the quality of penile inflow has been related directly to common vascular comorbidities, including age, diabetes mellitus, hypertension, atherosclerotic vascular diseases, hyperlipidemia, and cigarette smoking.³⁵ Another study, surveying men during hospitalization for myocardial infarction, showed 64% reported some degree of ED.⁶² There have also been reports showing an 18% prevalence of ED in men before experiencing a myocardial infarction, compared with 45% after the event.⁶³

Other conditions are commonly revealed during the clinical evaluation of patients with ED, including cigarette smoking, diabetes mellitus, chronic renal failure, and history of prostate cancer. Cigarette smoking deleteriously affects the arterial endothelium on a microvascular level and is a risk factor for other vascular disease states.^{64,65} A meta-analysis of the available literature over the last 20 years revealed that 40% of men with ED were smokers compared with 28% of men in the general population.⁶⁶

ED is present in at least 50% of men with diabetes mellitus, with the onset of symptoms occurring at an earlier age than in those without diabetes.⁶⁷ Several studies suggest that 26% to 35% of men with diabetes will develop ED.² In the MMAS, the age-adjusted probability of complete ED was 3 times higher in men who had treated diabetes mellitus than in men without diabetes.² There are several proposed mechanisms by which diabetes mellitus is thought to cause ED. Among these, diabetes-induced microvascular and atherosclerotic disease and diabetes-induced autonomic and somatic peripheral neuropathies seem to be the most important.⁶⁰ Chronic renal failure (CRF) is a risk factor for ED and should be revealed during a basic urologic evaluation. Effective treatment of CRF with renal transplantation reduces the severity of ED in these patients.⁶⁸

A common ED patient population encountered by the urologist includes those treated for prostate cancer by radical prostatectomy (open and laparoscopic/robotic), radiotherapy (external beam radiation therapy [XRT], intensity-modulated radiation therapy [IMRT], brachytherapy), hormonal therapy, and cryosurgery. A recent report indicates that there is more than a 50% incidence of ED after radical prostatectomy, regardless of whether a nerve-sparing procedure had been performed.⁶⁹ Other reports have shown that in younger men, bilateral nerve-sparing radical prostatectomy results in higher retention of baseline erectile function compared with the non-nerve sparing procedure.^{70,71} External-beam prostate radiotherapy and interstitial prostate brachytherapy also result in posttreatment ED, although typically less immediate in onset.⁷² Interstitial prostate cryosurgery is an emerging treatment modality for prostate cancer, but recent reports indicate a high likelihood of posttreatment ED.⁷³ Although the medical and surgical treatment of symptomatic benign prostate hyperplasia (BPH) is generally not harmful to the cavernosal nerves, reports show that sexual function may be adversely impacted, especially after the surgical treatment of BPH.⁷⁴

THE FIRST OFFICE VISIT

Patients may present independently to the urologist's office with a complaint of ED, may have been referred from a primary care provider, or may already have an established relationship for other urologic conditions (BPH/LUTS [lower urinary tract symptoms], calculi, and so forth). Studies have suggested, however, that the average man with ED waits up to 3 years before seeking medical evaluation (reinforcing the importance of the clinician initiating the discussion

regarding ED at each elective visit). In any case, a thorough, systematic evaluation of ED should start with a complete history and physical, including the identification of any risk factors for sexual dysfunction. Remember, ED is a couple's disease, affecting both the patients and their partners; therefore, their partners should be encouraged to be present during the office visit. Of primary importance is the building of a clinician-patient partnership established within an atmosphere of trust.⁷⁵

The visit should flow in a sequential manner, with each component generating and contributing information: (1) identify the chief complaint and sexual history; (2) a detailed medical and surgical history, including all comorbidities, medications and lifestyle factors; (3) a physical examination; (4) basic laboratory testing; (5) identification of the need for specialized evaluation and testing or referrals; and (6) treatment and reassessment (Box 1).

PATIENTS' HISTORY OF ED: THE CLINICAL ASSESSMENT

The first step in the evaluation of ED is a complete medical, social, and sexual history, recognizing

Box 1
Office-based ED work-up

- Always evaluate couple, together if possible
- Obtain a complete sexual history to define the ED
- Complete medical history
 - Comorbidities: cardiovascular disease, diabetes, hypertension, LUTS
 - Medications (especially antidepressants, antihypertensive agents)
 - Cigarette use/alcohol abuse/illicit drug use
- Complete surgical history (especially prior prostate surgery)
- Directed physical examination (gynecomastia, penile stretch, presence of Peyronie's plaques, testes consistency and size, digital rectal examination)
- Diagnostic tests
 - Blood tests include prostate-specific antigen, fasting glucose, testosterone, lipid panel
 - Assess hormonal status
 - Vascular assessment (intracavernous injection testing, possible penile duplex Doppler study)
 - Neurologic assessment (if indicated)

that ED may be a presenting symptom or marker of an associated disease state, such as cardiovascular disease. Any specific existing medical comorbidities, especially vascular and/or neurogenic, should be noted. A brief history of cardiovascular symptoms, including exercise tolerance, presence of angina, dyspnea, claudication, transient ischemic attacks, smoking history, and family history of cardiovascular disease, may identify patients with cardiac and vascular risk factors.⁷⁶ A detailed urologic history should be taken, with special attention to lower urinary tract symptoms, urologic trauma, urologic malignancies, urinary tract infections, and sexually transmitted infections. Prior urologic procedures (prostatectomy, BPH-related procedures, vasectomy) should be recorded as well as ED symptoms before, surrounding, and after those surgeries. An accurate medication list should be obtained, including herbal medicines, nutritional supplements, and other alternative therapies. Attention should be given to the documentation of any allergies and confirmation of any current nitrate usage. This time is also the point to inquire about any other drug use, illicit or supplemental, especially because numerous medications can cause ED.

The foundation to confirming the diagnosis and in evaluating patients' sexual function is a comprehensive sexual history. A validated pre-evaluation questionnaire can elucidate specific patient concerns and the need for further investigation. Assessing patients' sexual history should encompass any concerns regarding arousal, libido, performance, ejaculation and orgasm, and overall satisfaction. Levels of desire and libido should be addressed because these can also be important in identifying some symptoms of hypogonadism. A detailed inquiry should be made into the quality of the erections themselves. Patients should be asked about their ability to attain and maintain their erection, specifically about the inconsistencies in their erections (spontaneity, ability to maintain) and the progression of their problem. The clinician's goal in the process should be to differentiate between potential organic and psychogenic causes in a patient's sexual problem. The practitioner should also recognize any potential overlap between organic and psychogenic etiologies.

SYMPTOMS AND QUANTIFICATION

It is often difficult to quantify the symptoms of sexual dysfunction because of its variable nature and complex issues involving its cause. The practitioner should incorporate the use of ED symptom scales and questionnaires for patient

self-assessment whenever possible. There are many types of validated sexual questionnaires available for use.⁷⁷ Multidimensional questionnaires, such as the International Index of Erectile Function (IIEF) or the Sexual Health Inventory for Men, are very helpful in the identification of risk factors and potential causes of male sexual dysfunction. The IIEF may be used as a 5- or 15-item version to assess male sexual function over a 4-week period.²⁸ Single-item instruments have the advantage of high completion rates and low patient burden. On the other hand, multidimensional scales provide a broader and more complete assessment of disease severity. Despite such differences, similar results have been obtained across studies using these different measures. Symptom scales offer cost-efficient, validated measures for the identification of problems and also provide an assessment of past and current sexual function.⁷⁵

PHYSICAL EXAMINATION

On the first visit for ED, routine office vital signs should be taken and recorded, in addition to height and weight. The physical examination should include a broad screening for medical comorbid conditions relevant to ED, such as body habitus and blood pressure measurements. The medical history should help direct the examination of the organ systems, including a focused cardiovascular and neurologic examination. The urologic examination should include an assessment of proper development of secondary sexual characteristics; an abdominal and inguinal examination; and scrotal examination with assessment of testicular size, consistency, and any abnormal palpable or visual scrotal findings. The examination of the penis should include an assessment of cutaneous sensation as well as screening for any cutaneous lesions, congenital anomalies, traumatic lesions, or plaques. The penis should also be examined for stretched penile length, presence of a suprapubic or pelvic fat pad affecting such length, and any evidence of phimosis or penile adhesions and scarring. A proper digital rectal examination (DRE) should document prostate size, consistency, and the presence or absence of masses. The evaluation of cutaneous sensation in the perineum is useful in identifying potential neurogenic causes of ED.⁷⁸

BASIC LABORATORY EVALUATION

The goal of basic laboratory testing for ED is to perform cost-efficient screening for common systemic disorders. The Second International

Consultation on Sexual Dysfunction (2004) Committee on Sexual Dysfunction Assessment in Men has recommended that fasting blood glucose, fasting cholesterol and lipid panel, and testosterone levels be obtained routinely as part of a basic ED evaluation.⁷⁵ Other diagnostic laboratory values should be obtained when indicated specifically by the medical history and physical examination. These values include levels of prolactin, luteinizing hormone, follicle-stimulating hormone, prostate-specific antigen (PSA), complete blood count, and a thyroid function panel.

VASCULAR ASSESSMENT AND ADVANCED (SPECIALIZED) EVALUATION

Specialized evaluation of ED is often necessary to formally define its cause so that the practitioner may offer the most effective treatments. For many patients with ED, a detailed medical and sexual history, general medical examination with a focused genitourinary component, and a thorough review of all comorbidities and medications and laboratory evaluation can recognize the likely cause and allow the design of a treatment plan. Advanced or specialized evaluation is indicated if the initial treatments fail; if there is a diagnosis of PD; primary ED; history of pelvic or perineal trauma; in cases involving vascular or neurosurgical intervention; complicated endocrinopathy; complicated psychiatric disorder; complex relationship problems; when patients desire a better understanding of the underlying cause of the disease, especially as a marker of cardiovascular disease; and for medicolegal concerns.⁷⁵

Considerable research for the vascular assessment of ED over the past few decades has produced methods allowing for the quantitative and qualitative assessment of penile arterial and venoocclusive function. There are many tests available to evaluate penile vascular integrity, erectile function and anatomy, and venoocclusive function, including intracavernous injection (ICI) pharmacotesting, penile duplex Doppler ultrasonography (PDDU), dynamic infusion cavernosometry, and selective penile angiography, although the last two tests are typically not office based and are mentioned here for the sake of completeness.⁷⁵

The first-line in-office diagnostic test for vasculogenic ED has historically been the combination of ICI and visual sexual stimulation with direct assessment by an observer. This test bypasses both neurologic and hormonal influences and enables the direct evaluation of the vascular and physical status of the penis (ie, curvature). The ICI pharmacotest is simple to perform, minimally

invasive, and can be done relatively quickly in the office. The most common intracavernosal vasoactive agent used for this test is prostaglandin-E1 (PGE1). The initial dose should be 10 to 20 mcg for injection. Once the intracavernosal injection is administered, a subjective assessment of response should be documented: patients should give a visual rating of their erection, comparing it with their best erection at home. This rating allows a subjective assessment to be made between an inadequate versus adequate in-office erection. Redosing of vasoactive agents may be necessary to achieve the best (or bedroom) quality erection (BQE) because patient anxiety during testing situations may prevent achieving their BQE.

A normal result produced from an ICI pharmacotest in neurologically intact patients may suggest the diagnosis of psychogenic ED. According to Rosen and colleagues,⁷⁵ "comparison to other hemodynamic tests suggests a normal ICI pharmacotest is associated with normal venoocclusive function (flow to maintain rigidity values of 0.5–3 mL/min)." If the response from ICI pharmacotesting is insufficient, it may be difficult to distinguish pure arterial insufficiency from venoocclusive dysfunction. An abnormal ICI pharmacotest raises several diagnostic questions that may require further study. The clinician should be aware that an ICI pharmacotest alone might be a misleading diagnostic test to exclude vascular ED unless performed in combination with PDDU.⁷⁹ False-negative results can be found in almost 20% of patients with intermediate arterial inflow. False-positive results are also commonly known to occur. If the results are not thoroughly conclusive, or operative intervention is being considered, a second-line study is warranted.

PDDU

PDDU with vasoactive agents is the gold standard office-based diagnostic modality for determining the subtype of vasculogenic ED and in assessing the degree of its severity. The PDDU uses ICI and the assessment of penile vascular flow by color duplex Doppler ultrasound. It is the most informative and least invasive means of evaluating vasculogenic ED.⁷⁵ This test can be performed easily in the office setting, allowing for a direct and a quantifiable evaluation of ED and a useful baseline before therapy. The test provides an objective measurement of penile hemodynamics, especially arterial inflow. Ultrasonography may reveal other penile problems or anatomic genital abnormalities, such as PD. Another indication for PDDU is in preoperative planning to provide critical data for operations involving plaque grafts,

excisions, and even penile prostheses. It is also an effective test for demonstrating the classic arterial-lacunar fistula associated with high-flow arterial priapism.

To perform the study, one should have an understanding of the relevant penile anatomy and physiology of erection as well as their clinical correlations to ED. As with any procedure, a proper informed consent should be undertaken with patients outlining the purpose, alternatives, risks, and benefits of the testing process. The examination room should be comfortable and safe from intrusion and distraction. False-positive test results, displayed as a partial erection when there is no underlying vascular abnormality, may be secondary to patient anxiety, needle phobia, and/or inadequate medication dosage. Although PDDU is a noninvasive testing modality, ICIs do have potential morbidity that the examiner and patients should be aware of. Up to 20% of neurologically intact men report aching in the penis after PGE1 injections. Prolonged erection is another well-known risk and should be pharmacologically reversed with dilute intracorporeal phenylephrine injections to avoid priapism and its subsequent morbidity.

To perform the study in the office, a high-resolution ultrasonographic probe (7–10 MHz) is required for real-time ultrasonography and color pulsed Doppler, which allows the examiner to evaluate penile blood flow changes throughout the various phases of erection. With color-coded duplex sonography, the direction of blood flow is designated with red (toward the probe) or blue (away from the probe), making identification of the small cavernous vessels and recording of blood flow easier.^{80,81} Following intracorporeal injection of the vasoactive medication, baseline penile blood flow measurements are taken and subsequently measured at approximately 5-minute intervals until BQE is achieved, with redosing as necessary; resolution of the erection is then documented. Dosing information during the study is also useful as a basis for intracavernosal therapy.⁸² Studies have demonstrated the combination of injection plus manual self-stimulation leads to higher rates of rigid erections compared with injection alone.⁸³ For recording purposes, a recent validated scale, the Erection Hardness Score (scale 1–4), can be used to standardize responses.⁸⁴ If necessary, patients should be reexamined after self-stimulation.^{85,86}

The combination of oral sildenafil citrate and a visual erotic stimulation has also been studied as an effective noninvasive pharmacologic induction of erection.⁸⁷ Studies are mixed regarding a comparable increase in the peak flow velocities as is

achieved with ICI; the time frame is considerably longer, up to 90 minutes after an oral medication is given. This method may be useful in predicting treatment success with phosphodiesterase inhibitors (PDE5Is).^{88–90}

The important vascular parameters assessed by PDDU include cavernous artery diameters, peak systolic velocity (PSV), and end-diastolic arterial velocity. Normal cavernous arterial flow is defined as a PSV greater than 30 cm/s. A PSV measurement of less than 25 cm/s following ICI pharmacotesting and erotic stimuli has 100% sensitivity and 95% specificity in selecting patients with abnormal penile arteriography.⁷⁵ Cavernous venous occlusive disease (CVOD) is defined as the inability to achieve and maintain adequate erections despite appropriate arterial inflow.^{83–85,91,92} Many investigators include another value that takes PSV into account. This value is the resistive index (RI). The formula for RI is as follows: $RI = (PSV - EDV) / PSV$, where EDV is the end-diastolic velocity. As the penile pressure equals or exceeds the diastolic pressure, the diastolic flow in the corpora (EDV) approaches zero and the value for RI approaches 1. During the initial tumescence phase, as well as in partial erections, the diastolic flow remains and the RI value is less than 1.0. Naroda and colleagues^{93,94} concluded that an RI of less than 0.75 predicts CVOD in nearly 95% of patients and that an RI greater than 0.9 to 1 is normal.

Doppler evaluations should include measurements for the evaluation of blood flow as well as any physical deformity noted (such as plaques and penile curvature). Once patients reach full tumescence (or BQE), gray-scale imaging for the presence of nonvascular abnormalities, such as plaques, curvature, and fibrosis, should be performed. At the conclusion of the testing period, it is important to ensure complete detumescence. Occasionally, this will require an intracorporeal injection of a diluted phenylephrine solution, which may be repeated at approximately 5-minute intervals as needed, until detumescence is achieved. Alternate agents, including epinephrine, have also been used, although some providers use cardiac monitoring during this process because of their potent and possibly systemic effects. These patients should be monitored for symptoms of acute hypertension, tachycardia, arrhythmias, and palpitations.

NEUROLOGIC EVALUATION

A patient's medical history and physical examination develops the foundation for further neurologic evaluation of ED. Generally, many studies have shown that specialized testing for neurogenic ED

is only indicated in cases of underlying neurogenic disease or when normal vascular studies and history suggest a neurologic cause. Neurogenic ED usually involves the following: known neurologic risk factors, younger age at presentation, acute onset of ED, and a normal or excellent response following ICI or oral PDE5 inhibitor pharmacotesting. Although specific neurologic tests are available, evidence suggests that they lack adequate sensitivity and reliability for routine clinical diagnosis.⁷⁵ Various testing measures include nerve conduction velocity studies, biothesiometry, bulbocavernosus electromyography (EMG), and corpus cavernosa EMG. One study by Lefaucheur and colleagues⁹⁵ did show a strong correlation between abnormal penile thermal sensory testing with the clinical diagnosis of neurogenic ED. However, further evaluations are necessary before this test may be brought into routine clinical practice.

PSYCHOLOGICAL EVALUATION

Most screening evaluations for ED can identify psychological risk factors, both independently and in coexistence with other organic risk factors. Patients (often times with their partners) with a psychogenic component or primary psychogenic sexual dysfunction should be referred to those practitioners with specific expertise (psychiatrists, clinical psychologists, and sex therapists) as part of their management.

OFFICE TREATMENT OF ED

Once a diagnosis of ED has been made, the next step in management is to choose the appropriate treatment plan. There is no single treatment that is appropriate for every patient, and an individual treatment plan should be discussed with patients and their partners to assure the best level of satisfaction. Treatment can be considered in terms of first-, second-, and third-line therapies (Box 2). First-line therapies include addressing reversible lifestyle issues (smoking cessation, healthy diet, alcohol moderation, and exercise), correcting hormonal abnormalities, and simple noninvasive therapies, such as oral medications and vacuum devices. Second-line therapies involve more invasive options, including intracorporeal injection therapy and intraurethral medication. Third-line treatments are not considered as office-based therapies, including surgical implantation of penile prosthesis and penile revascularization, and are typically reserved for those patients who cannot achieve satisfaction with less-invasive therapies (and are not discussed here).

Box 2
Therapeutic options for ED

- First-line therapeutic options
 - Address reversible lifestyle issues
 - Psychosexual therapy, when indicated
 - Oral therapy: PDE5 inhibitors (daily or on demand)
 - Vacuum erection devices
- Second-line therapeutic options
 - ICI therapy
 - Intraurethral therapy
 - Combination therapy
- Third-line therapeutic options
 - Surgery
 - Implantation of penile prosthesis
 - Penile revascularization

HORMONAL REPLACEMENT THERAPY

Testosterone replacement therapy should only be used in the treatment of sexual dysfunction in the presence of symptomatic hypogonadism and is based on repeat values from early morning specimens of low serum testosterone levels (Box 3). In these cases, testosterone replacement is used to maintain normal serum levels of testosterone in an attempt to restore potency and libido. In addition, maintenance of muscle mass and bone density may be achieved. Because of the potential side effects and relatively unpredictable serum levels obtained by oral administration of testosterone preparations, parenteral administration is preferred.

Currently, there are multiple testosterone formulations available for the treatment of hypogonadism. These formulations include intramuscular testosterone, buccal testosterone, topical gels and patches, and time-released testosterone pellets. Intramuscular testosterone is typically administered in dosages of 200 to 300 mg every 2 to 3 weeks. The amount and frequency of administration will vary with the individual and can be titrated. Topical and buccal administration must be used on a daily basis and may offer more stable hormone levels as compared with intramuscular therapy. Considerations of drug transference (ie, to spouse or children) and local skin reactions are issues of concern associated with topical agents. Testosterone pellets can also be placed under the skin (typically in the hip or buttocks), and their effectiveness lasts an average of 3 to 6 months.

Box 3**Office-based management of low testosterone**

- Clinical presenting symptoms often seen in patients with low testosterone
 - Decreased sexual function
 - Poor libido, lack of interest
 - Decreased energy levels, fatigue, depression
- Other possible effects of decreased testosterone levels
 - Medical ED treatments (PDE5Is) may be less effective
 - Decreased muscle mass and bone density
 - Potential adverse effects on memory and cardiovascular function
- Therapeutic measures include
 - Assure low morning testosterone; normal PSA and DRE
 - Testosterone enanthate intramuscular every 1 to 3 weeks (in office or home use)
 - Topical therapy, including gels or patches (used daily)
 - Testosterone pellets (in office, every 4–6 months)
 - Monitor testosterone, PSA, lipids, complete blood count (CBC) on regular basis; adjust dose or change regimen as indicated

This form of treatment eliminates the need for daily treatment (improving convenience for some men) and eliminates the risk of transference.

Of note, all forms of testosterone replacement therapy may have some risks of increasing BPH symptoms, a rising PSA, and potentially increasing stroke risk. Regular close monitoring of hormone levels, PSA, CBC, and lipids is recommended. Finally, hormone replacement therapy is relatively contraindicated in men with untreated adenocarcinoma of the prostate or breast because administration may increase the rate of growth of their cancer. It would, therefore, seem prudent that before beginning testosterone replacement therapy in men older than 40 years, serum PSA levels, a DRE, and possibly transrectal ultrasound studies should be performed.

Hyperprolactinemia, another hormonal abnormality effecting sexual function, is treated by (1) cessation of medication causing hyperprolactinemia (eg, estrogens, alpha methyl dopa), (2) administration of bromocriptine, or (3) surgical ablation or extirpation of a pituitary prolactin secreting tumor. Treatment with exogenous testosterone to

restore the diminished levels of serum testosterone usually seen with this disorder has not been demonstrated to reverse the ED.

ORAL AGENTS: PDE5IS

In order for a normal erection to occur, an interrelated sequence of events that leads to vascular smooth muscle relaxation is necessary. Nitric oxide (NO), produced by vascular endothelial cells and nonadrenergic/noncholinergic neurons, is released and taken up by vascular smooth muscle cells. The level and activity of NO synthase is under the partial influence of testosterone. NO activates the enzyme guanylate cyclase, catalyzing the conversion of guanosine triphosphate into cyclic guanosine monophosphate (cGMP), which then acts as a second messenger with multiple intracellular effects; the most important effect with regard to erectile function is a decrease in intracellular calcium ion concentration, which facilitates smooth muscle relaxation. Unfortunately, the activity of cGMP is limited by its reconversion into GMP PDE5. PDE5Is suppress this pathway, resulting in higher intracellular levels of the second messenger, cGMP, and increased smooth muscle relaxation.

This important discovery has led to the development of specific PDE5I agents that are effective in the treatment of ED. These oral agents include sildenafil, vardenafil, tadalafil, and avanafil and are highly specific for PDE5, with efficacies approaching 60%. The pharmacokinetic properties of these agents differ, resulting in changes in their half-life (T_{1/2}), which effects their period of efficacy. In addition, because there are differences in the degree of selectivity for the various agents, there is the possibility of cross-reactivity with different phosphodiesterases in other parts of the body, such as muscle and retina. As compared with other ED treatments, the PDE5I agents offer certain advantages: they are oral medications, and patients and partners place a high priority on this; they are well tolerated; they require stimulation; and daily agents improve spontaneity. The disadvantages include decreased efficacy in severe ED cases, as compared with other therapies; the need for systemic administration; an absolute contraindication with nitrates; delayed time of onset of action; high cost; and class-specific side effects (SEs), including headache, flushing, rhinitis, dyspepsia, occasional visual changes, and muscle pain.

VACUUM ERECTION DEVICES

Vacuum erection devices (VEDs) are a noninvasive and viable therapeutic option and may be offered

as a first-line of treatment of patients with ED. Most VEDs have 3 common components: a vacuum cylinder, a vacuum pump that creates negative pressure within the chamber, and a constrictor or tension band that is applied to the base of the penis after the erection is achieved. The erection resulting from the vacuum device differs from the physiologically induced erection. The latter type is achieved by the initial relaxation of the corporal smooth musculature, thus allowing for engorgement of blood into the lacunar spaces. In the case of a vacuum-induced erection, corporal smooth muscle relaxation does not occur initially and blood is simply trapped in both the intracorporeal and extracorporeal compartments of the penis.

Complications associated with the use of a VED may include difficulty with ejaculation, penile pain, ecchymosis, hematomas, and petechiae (especially if the device is used for more than 30 minutes). Patients taking aspirin or warfarin sodium are more likely to develop vascular complications. Finally, only physician-prescribed, pressure-regulated VEDs should be used in the treatment of ED. Severe morbidities, including the development of PD and worsening of ED, are more likely to occur with the use of commercial, nonprescription, magazine-ad-type devices that lack the pop-off pressure mechanism that is incorporated in the prescription devices.

INTRACAVERNOSAL INJECTION OF VASOACTIVE AGENTS

An effective therapeutic option for men with ED is intracavernosal pharmacotherapy. These self-administered intracavernosal injections of vasoactive agents serve either to directly relax the corporal smooth musculature or block adrenergic tone of the corporal smooth muscle and involve the use of papaverine hydrochloride, phentolamine mesylate, and the prostanoid prostaglandin E₁. The mechanism of action of papaverine hydrochloride and prostaglandin E₁ is via direct smooth muscle relaxation. Therefore, when injected intracavernosally, they maximize arterial inflow as well as corporal venoocclusion via the relaxation of both arterial and trabecular smooth musculature, respectively. Phentolamine, on the other hand, blocks adrenergically induced muscle tone and, therefore, does not, alone, initiate erections but is effective in prolonging the erectile response. A variety of solutions containing the aforementioned agents are presently being used in clinical practice: papaverine alone, papaverine and phentolamine, prostaglandin E₁ alone, phentolamine and prostaglandin E₁, or a mixture of all 3 (papaverine, prostaglandin E₁, phentolamine).

In general, intracavernosal pharmacotherapy, like vacuum constrictor therapy, may be offered to most patients with organic ED, although patients with poor manual dexterity, poor visual acuity, morbid obesity, or those in whom a transient hypotensive episode may have a deleterious effect (eg, unstable cardiovascular disease and transient ischemic attacks) should be carefully screened before being offered this therapeutic option. Successful treatment of impotence with this therapy has been achieved in patients with diabetes concomitantly taking aspirin or warfarin sodium. Patients with significant psychiatric disease or potential for misuse or abuse of this therapy should be excluded from treatment. The usual therapeutic goal is to be able to create a rigid enough erection satisfactory for vaginal penetration that lasts between 30 minutes and 1 hour.

The initial objective of the dosage determination phase is to define the lowest dose required for achieving an appropriate erectile response. Patients are injected at first in the office with low doses, which are then increased incrementally. After an appropriate dose has been determined and detumescence observed, patients are instructed in proper injection techniques by reviewing printed material showing them the site and sterile technique of injection. An insulin syringe with a 27- to 30-gauge needle is usually used, which minimizes pain and bleeding. Patients are also taught to compress the site of injection for 3 minutes following therapy. Patients are told not to inject more frequently than 3 times per week. Those patients who enter a pharmacologic erection program should first understand a detailed informed consent, which states the known complications of this treatment and discusses the possibility of significant side effects, including nodules, plaques, curvature, and priapism. Patients must be cautioned to seek immediate medical care if an erection persists for 4 hours or longer.

MEDICAL URETHRAL SYSTEM FOR ERECTION

The medical urethral system for erection (MUSE) is a safe and effective formulation of PGE₁, which causes erection by inducing the formation of cAMP in the erectile tissue. MUSE is formulated into a pellet, which the man places into the tip of the penis, via the meatus, into the distal urethra, before sexual activity. After manipulation of the penis, the medication is absorbed into the erectile tissue and leads to penile engorgement. The main advantages of the MUSE system are that it involves no needles or injections, it is safe and effective, and the erection typically occurs within 10 to 15 minutes. There are, however, significant

disadvantages for some men, including penile pain and burning (caused, in part, by the high doses of PGE1 required for absorption); occasional hypotension; often inadequate penile rigidity, sometimes necessitating the use of a constriction band; the high cost; the fact that it should be refrigerated before use; and the actual procedure of administration may be difficult for some men.

THIRD-LINE TREATMENT OPTIONS

Despite excellent office-based first- and second-line management options for ED, some patients require a third-line treatment to restore their sexual function and quality of life: implantation of a penile prosthesis. The safety, longevity, and success of these devices have currently reached an all-time high. There are fewer mechanical malfunctions and a lower incidence of infection rates (leading to and maintaining the highest patient and partner satisfaction measures of all ED therapies) and should be considered for any patient with ED that does not achieve a satisfactory response to first- or second-line treatment alternatives.

PENILE REHABILITATION

Penile rehabilitation refers to the management of ED in men following radical prostatectomy. Although many of these men may have had normal erectile function before surgery, despite bilateral nerve-sparing procedures and robotic surgery, a significant percentage of these men will notice a decrease in their erectile function and penile length postoperatively. The goal of penile rehabilitation in theory is to minimize these detrimental effects of surgery, maximize sexual function, and improve quality of life. Although there is no accepted universal algorithm for penile rehabilitation, it is generally accepted that by starting early in the postoperative phase (weeks, not months), using a combination of oral agents (daily when possible) or ICI (when oral agents fail), in addition to the application daily of the VED, patients may be able to maximize their restoration of function. Further studies are necessary to determine the ideal therapeutic regimen.

SUMMARY

The introduction of PDE5Is has broadened the scope of ED evaluations to include primary care providers, urologists, cardiovascular specialists, endocrinologists, neurologists, psychiatrists, psychologists, and other specialties. A multidisciplinary approach is vital to patients with ED seeking evaluation and treatment. A systematic approach in the clinical evaluation of ED should

identify sexual problems through the appropriate use of questionnaires and symptom scales, a detailed medical and sexual history, directed physical examination, and basic laboratory testing. For proper diagnosis, the practitioner must be aware of all medical comorbidities associated with ED. Along with in-office diagnostic testing, patients will be able to understand the cause and nature of their ED, and physicians will be able to offer the most appropriate and successful treatments.

OFFICE-BASED MANAGEMENT OF PD

PD is a male sexual disorder that may be associated with ED, pain with erections, and penile curvature. It is a condition involving the tunica albuginea of the corporal bodies. It is characterized by the formation of plaques of fibrous tissue that results in various severities of penile curvature. In some men, there is significant ED or severe curvature that precludes sexual intercourse. This section reviews the potential mechanisms of PD as well as the current office-based evaluation and treatment options for PD.

BACKGROUND AND CAUSE

Francois de la Peyronie⁹⁶ first described "induration penis plastic" in 1743 and was the first to offer the treatment of what is now known as PD. PD is now generally thought to be a fibrotic wound-healing disorder of the tunica albuginea. The true pathophysiology of PD and the mechanism of plaque formation are unknown. What is known is that this plaque formation results in penile deformity, curvature, hinging, narrowing, shortening, and painful erections. PD is not only a physically but also a psychologically devastating disorder for these men and is essentially a disease of fibrosis. One model of disease is centered on repeated microtrauma in genetically susceptible individuals. The localized response to injury releases endogenous factors (such as transforming growth factor beta [TGF- β]). This response can lead to the biologic transformation of cells within the tunica albuginea; cell-cycle dysregulation; genotypic changes; and increased expression of cytokines and free radicals that can lead to unregulated extracellular matrix deposition, including fibronectin and collagen, and ultimately plaque formation. This plaque, which does not seem to undergo proper scar remodeling, results in an inelastic segment in the involved tunica albuginea.⁹⁷⁻¹⁰⁵ Some other theories included infection, such as sexually transmitted diseases (gonorrhea and syphilis).^{106,107} The most common theory among

researchers is that PD is a disorder of wound healing, with repetitive microtrauma as a causative origin.¹⁰⁸ From this paradigm, much research has been performed into the immunologic, biochemical, and cytogenetic factors that may play a role in plaque formation.^{109,110} As initially reported by Abernathy¹⁰⁷ in 1828, Dupuytren contracture may be associated with PD, and the pathophysiologic pathways in both seem similar. In both conditions, collagen synthesis is abnormally increased with respect to collagen breakdown. It is through this mechanism that the cells responsible for the collagen synthesis and wound contraction (myofibroblasts) seem to occur in excessive amounts. This excess activates an abnormal response to local injury in a man with genetic predisposition to abnormal scar formation and healing. As part of the routine examination in patients with PD, patients' hands should be evaluated for evidence of contracture.

The process of wound healing is divided into 3 phases. The acute phase is described to involve enzymatic cleanup of dead, damaged, or infected tissue with concurrent release of cytokines. Fibrin then is generated and deposited into tissues, including the tunica albuginea in men with PD, and has been proposed to result in the persistent stimulation of scar formation. Overexpression of other cytokines, such as TGF- β , may also play a role. The second phase encompasses strengthening or repairing the wound through scar formation. With normal individuals, cytokines activate the migration of fibroblasts and macrophages. In PD, these fibroblasts may differentiate to become myofibroblasts, which can respond differently to injury. In the final (contractile) phase of wound healing, the scar undergoes remodeling. At this time, metalloproteinases are released (collagenases and gelatinases), remodeling the tissue. This action results in a smaller, more organized scar. Patients with PD may have atypical amounts or dysfunctional types of these collagenases, causing the abnormal plaque or scar.¹¹¹

EPIDEMIOLOGY

Accurate epidemiologic information regarding PD is limited. Polkey¹¹² first published data in 1928, with 550 case reports. In 1968, Ludvik and Wasserburger¹¹³ described experience within a private clinic, with a prevalence rate of 0.3% to 0.7%. Thirty years later, Devine¹¹⁴ reported a prevalence of symptomatic PD in 2 populations of male physicians of approximately 1%. The first cross-sectional study was provided in a report by Lindsay and colleagues¹¹⁵ in 1991, showing the proposed incidence and prevalence rates of PD of

0.38%. Recent studies suggest that the actual prevalence rate may be closer to 9% or even higher. In a study by Mulhall and colleagues¹¹⁶ in 2004, of the 534 men presenting to a group of geographically diffuse urologists in the United States for prostate cancer screening, 8.9% were found to have objective evidence of PD. The impact of PD is probably not accurately represented in common urologic practice because the true prevalence rate may be even higher and easily underestimated because patients are likely to underreport such a condition that causes embarrassment. Disparity also exists regarding the natural history of PD, which was initially thought to be a disease of spontaneous resolution; however, recent studies have dispelled this myth.^{117–119} Another popular misconception is that PD is mainly a disease of older men. PD has been reported to occur over a wide range of ages, with reports in patients as young as 18 years.^{120,121}

EVALUATION AND TREATMENT

The first step in the evaluation of men with PD should include a complete medical and sexual history, including duration of onset, history of trauma, degree of curvature, loss of penile length, penile pain (and resolution), degree of erectile function, and the ability to have comfortable intercourse. A detailed physical examination should describe the presence of any palpable plaque, tenderness, numbness, and decreased penile stretch. PDDU is helpful to objectively document the degree of penile curvature, narrowing, or other anatomic abnormality, as well as to objectively define the degree of erectile function. This information is critical to document before any intervention. Several nonsurgical options are currently being used in the treatment of PD, which may reduce or stabilize objective measures, such as penile curvature and erectile function, and also improve subjective measures, such as sexual satisfaction, pain, and partner satisfaction. In addition, oral PDE5I agents are often used as a component of the treatment regimen in these patients.^{117,122–124}

MEDICAL THERAPY OF PD

Many medical therapies have been described in the search for a successful treatment regimen for PD. Certain medical treatments are based on anecdotal experiences because existing studies are characterized by small numbers of patients with limited follow-up; the absence of placebo or control groups; and few, if any, objective measures of improvement. Another confounding issue

is the reporting of spontaneous remission rates, ranging from 7% to 29%.^{117,125,126}

VITAMIN E

Vitamin E was one of the first oral therapies to be described in the treatment of PD. Initially studied by Scott and Scardino¹²⁷ in 1948, vitamin E was suspected to be of clinical value because of its mechanism of limiting oxidative stress of reactive oxygen species, which increase during the acute and proliferative phases of wound healing.^{127,128} The antioxidant properties of vitamin E were thought to be helpful against the prolonged inflammatory phase of wound healing, previously demonstrated in PD.^{99,128} Despite multiple studies looking at the use of vitamin E in these patients, a review of the literature reveals no large placebo-controlled trials with vitamin E demonstrating any true benefit in the treatment of PD. That knowledge, paired with the evidence that high doses of vitamin E may increase the risk of cerebrovascular events, does not support its continued empiric use in PD.^{129–131}

COLCHICINE

Colchicine, first proposed by in 1994 for the treatment of PD, was thought to hinder fibrosis and collagen deposition primarily by inhibiting neutrophil microtubules.¹³² Several small studies, including the only randomized trial examining the effects of colchicine as a monotherapy, revealed that colchicine was no better than placebo in improving pain, curvature, or plaque size.^{133–135} With its lack of demonstrable efficacy and a significant side effect profile (gastrointestinal distress, diarrhea, aplastic anemia), the authors do not recommend colchicine as a therapy for PD.

POTASSIUM AMINO BENZOATE

Another oral agent used in the therapy for PD is potassium aminobenzoate, which is thought to increase the activity of monoamine oxidase in tissues, thereby decreasing local levels of serotonin, which may contribute to fibrogenesis and scar formation. A review of the literature did not reveal any large, placebo-controlled studies demonstrating its efficacy in the treatment of PD.^{136–140} In addition, this drug is costly, can require taking up to 24 tablets daily, and is known for its low tolerability caused by the gastrointestinal side effects. With its limited evidence of benefit, increased side effect profile, and inconvenient administration regimen, most experts do not support the use of potassium aminobenzoate as a treatment of PD.

TAMOXIFEN CITRATE AND CARNITINE

Tamoxifen is a selective estrogen receptor modulator that has both agonist and antagonist effects on target tissues depending on tissue-specific estrogen receptor expression. Tamoxifen is also reported to affect the release of TGF from fibroblasts, blocking TGF receptors, thus potentially reducing fibrogenesis.^{141–144} Carnitine, a naturally occurring metabolic intermediate, works via the inhibition of acetyl coenzyme A, may help in the repair of damaged cells, and has been proposed as a treatment of PD. A review of the literature did not reveal any large, placebo-controlled studies demonstrating improvement in pain, curvature, or plaque size in the treatment of PD for either agent; they are not currently recommended for the treatment of PD.

PENTOXIFYLLINE

Pentoxifylline (PTX) is a nonspecific phosphodiesterase inhibitor, with combined antiinflammatory and antifibrogenic properties by downregulating TGF- β and increasing fibrinolytic activity. Its use has been suggested in the management in PD, after studies have shown its effects in vitro to attenuate both collagen fiber deposition and elastogenesis.^{145,146} Although small, uncontrolled studies suggested some improvement in penile curvature, this has not been demonstrated in large, placebo-controlled trials. In addition, patients taking PTX may experience significant side effects, including nausea, vomiting, dyspepsia, and diarrhea.^{147,148} Further randomized, placebo-controlled trials are necessary before recommending this as an effective treatment option for PD.

In summary, no oral therapy to date has been shown to reliably reduce penile deformity in a clinically meaningful way. The 2010 published guidelines on PD by Ralph and colleagues¹⁴⁹ state: "There is evidence that there is no benefit with respect to deformity reduction with any oral therapy, including vitamin E, potassium aminobenzoate, colchicine, Tamoxifen, and Carnitine."

TOPICAL THERAPY

Verapamil as a treatment of PD has been suggested, in part, based on studies demonstrating that exocytosis of extracellular matrix molecules, including collagen, fibronectin, and glycosaminoglycan, is a calcium ion-dependent process.¹⁵⁰ Aggeler and colleagues¹⁵¹ noted changes in cell shape when fibroblasts were exposed to calcium antagonists in vitro, associated with increased

extracellular matrix collagenase secretion, and decreased collagen and fibronectin synthesis and secretion.¹⁵² In 2002, Martin and colleagues¹⁵³ initiated a study to confirm that topically applied verapamil gel could penetrate into the tissues of the tunica albuginea. This research investigated tissue concentrations in men who were exposed to topical verapamil gel before penile prosthesis implantation surgery. At the time of prosthetic implantation, a sample of tunica albuginea was excised and analyzed. No verapamil was detected in the tunica albuginea specimens, leading the investigators to conclude that transdermal application of topical verapamil has no scientific basis.¹⁵³ In addition, no controlled trial has been performed demonstrating the benefit of topical verapamil.

INTRALESIONAL THERAPY

Steroids

Teasley¹⁵⁴ described the first use of intralesional steroids for PD in 1954. However, despite multiple studies, objective efficacy in the treatment of PD has not been demonstrated.^{154–157} Currently, the treatment of PD with intralesional steroid injections is discouraged. There are no consistent beneficial effects of this treatment, and local tissue may atrophy. Of note, steroid use can distort tissue planes between Buck fascia and the tunica albuginea, making subsequent surgical correction more difficult.

Collagenase

Collagen, specifically type I and III collagen, has been established as the primary component of the dense, fibrotic PD plaque and collagenase is the enzyme that catalyzes the breakdown of collagen. Gelbard and colleagues^{158,159} were the first to study clostridial collagenase in vitro for the treatment of PD in 1982. Their early results reported objective improvement in 20 (64%) of 31 patients within 4 weeks of treatment with collagenase injections.¹⁶⁰ A double-blind, placebo-controlled trial demonstrated a statistically significant improvement in curvature in the collagenase-treated group, documenting the efficacy and safety of intralesional clostridial collagenase injection therapy. The most common adverse events (edema, penile pain, and ecchymosis) occurred in 20 (80%) patients.¹⁶¹ Collagenase clostridium histolyticum is currently in large-scale, multicenter, randomized, placebo-controlled trials and is awaiting US Food and Drug Administration approval for the treatment of PD.

Verapamil

Levine¹⁶² first reported the use of intralesional verapamil, a calcium channel blocker in 1994. In their initial nonrandomized study, 14 men received biweekly injections of verapamil into their Peyronie's plaques for 6 months. Subjectively, there was significant improvement in plaque-associated penile narrowing in all patients (100%) and improvement in curvature in 6 (42%). Objectively, a decreased plaque volume of more than 50% was noted in 4 (30%) of the patients. Plaque softening was noted in all patients; 12 patients (83%) noticed that plaque-related changes in erectile function had improved. No adverse effects were noted.¹⁶² A second trial of men with early stage disease, (PD <1 year) demonstrated a rapid reduction of pain after a mean of 2.5 injections in 97% of men, with improvement in sexual function, reduction in deformity, and a mean reduction of curvature in 65% of patients. In late-stage disease, (PD >1 year) Levine reported that intralesional verapamil decreased curvature in 8 men (44%).¹⁰⁸ The third trial was the largest published single-center trial using intralesional verapamil. This trial was a prospective nonrandomized study of 140 men (mean duration of disease of 17.7 months), with 77.5% of the patients documented as receiving previous therapy with vitamin E, potassium aminobenzoate, or colchicine. In this study, a local penile block using 0.5% bupivacaine (10–20 mL) was administered at the base of the penis. Next, using a short (five-eighths in) needle (25-gauge to prevent needle breakage), 1 to 5 punctures were made through the skin. However, multiple passes were made through the plaque as verapamil was delivered, with the goal of leaving the drug in the tracks. A standardized dose of 10 mg verapamil (5 mg/2 mL), diluted to 10 mL total volume with injectable saline, was used for injection. Each set of injections was administered at a prescribed interval of 2 weeks for a total of 12 treatment sessions. Of the 121 men tested, penile curvature decreased in 73 (60%), increased in 10 (8%), and remained unchanged in 38 (31%).¹⁶³ In these studies, the patients received 12 biweekly injections over 6 months. The rationale by Levine and colleagues is that scar remodeling occurs at glacial speed, suggesting that repeated treatment over time would produce better results. Bennett and colleagues¹⁶⁴ evaluated intralesional verapamil biweekly and reported curve improvement in 22%; they stated that 60% showed no disease progression, suggesting a stabilizing effect. Rehman and colleagues¹⁶⁵ published the first randomized single-blind trial of intralesional injection of verapamil versus saline, in 14 patients and

reported significant differences in subjective improvement in quality of erections and objective measurements of plaque volume. A nonsignificant improvement trend was also noted in degree of curvature in the verapamil group.

Recently nicardipine, also a calcium channel blocker, was compared with saline injection as a potential treatment of PD. Although significant improvement in penile curvature was seen in both the nicardipine and saline groups, a significant reduction in the IIEF-5 score and in plaque size was seen only in the nicardipine group.¹⁶⁶ In 2009, a randomized, single-blind, placebo-controlled trial comparing intralesional verapamil with saline did not demonstrate any significant improvements in penile deformity, pain, plaque softening, or sexual function in either groups.¹⁶⁷ Although there are limited controlled data showing clear benefit with intralesional verapamil, the larger-scale trials suggest a curvature improvement rate in up to 60% of men completing 12 injections. Currently, the recommended regimen in experts that use verapamil is a trial of 6 injections, with each injection occurring every 2 weeks. If no improvement is noted, they suggest the injection therapy may be terminated, the dose of verapamil increased to 20 mg (in men with no cardiovascular disease), or interferon (IFN) injections may be offered.

IFN

The potential for the use of intralesional IFN as a therapy for PD was first demonstrated by Duncan and colleagues¹⁶⁸ in 1991. These investigators reported that IFN α , β , and γ decreased the rate of proliferation of fibroblasts in Peyronie's plaques in vitro as well as reduced the production of extracellular collagen and increased the activity of collagenase. Initial clinical trials published by Wegner and colleagues^{169,170} in 1995 and 1997 demonstrated a significant incidence of side effects, specifically myalgia and fever. In 1997, Judge and Wisniewski¹⁷¹ published the results of their study in which the dose of IFN was modified, resulting in improvements in the side effects. Ahuja and colleagues¹⁷² performed a nonrandomized study of 20 men who received 1 million units biweekly for 6 months. In this trial, 100% of the men had softening of the plaque, 90% of those presenting with pain had improvement, and 55% had a subjective reduction in plaque size. In 2004, Dang and colleagues¹⁷³ administered a reduced dosage of IFN (2×10^6 U) biweekly for 6 weeks. Objective improvements in curvature, using pharmacologic stimulation and a protractor, of greater than 20% were noted in 67% of men. Of those presenting with pain, 80% claimed

improvement, and 71% with presenting complaints of ED also noted improvement in function. In 2006, Hellstrom and colleagues¹⁷⁴ reported their multicenter, single-blind, placebo-controlled trial of 117 men with PD, with a duration of disease for more than 12 months. This trial was the first placebo-controlled trial of intralesional injection therapy for PD to offer evidence of treatment benefit. These men underwent 6 biweekly injections of either IFN- α 2b or saline, for a total of 12 weeks.¹⁴⁸ Average curvature in the treatment group improved 13° versus 4° in the placebo arm. Pain resolution was noted in 67% of the treatment patients versus 28% for the placebo. Pretreatment nonsteroidal antiinflammatory drugs (NSAIDs) and assuring excellent hydration during therapy significantly reduced the degree of flu-like SEs. Further investigation is clearly needed regarding IFN therapy as well as the possible effects of plaque injection in general because it seems that saline injection itself may offer some benefit to certain patients.¹⁷⁵

External Energy Therapy

Local penile electro-shockwave therapy (ESWT) has been suggested as a treatment option for PD. The proposed mechanism of action involves direct damage to the plaque resulting in an inflammatory reaction. This reaction is thought to increase macrophage activity leading to lysis of the plaque. ESWT is also hypothesized to improve vascularity, resulting in plaque resorption and to create contralateral scarring, resulting in false straightening.¹⁷⁶ In most studies, the efficacy of ESWT is limited to only subjective reports of improvement of deformity, plaque size, or pain.^{177–180} At this time, published studies have not shown reliable clinical benefit in terms of curvature, plaque size, or objective improvement in sexual function or rigidity. The International Consultation on Sexual Medicine's (ICSM's) guidelines state: "There is evidence that ESWT does not improve PD related deformity."¹⁴⁸

Iontophoresis

Iontophoresis is the use of electric current to transport ions through tissue. This current has been studied and used in dermatology to induce wound healing.¹⁸¹ Levine and colleagues¹⁸² verified the efficacy of this mode of transmission of verapamil in 2002 using surgically retrieved tunica albuginea specimens after a single intraoperative exposure before partial plaque excision and grafting surgery. In 2009, Stancik and colleagues¹⁸³ compared excised-treated Peyronie's plaques to therapy naive plaques. They demonstrated a

decreased expression of basic fibroblast growth factor (bFGF), mRNA, and bFGF protein expression in excised Peyronie's plaques after having undergone electromotive drug therapy with dexamethasone, verapamil, and lidocaine. Greenfield and colleagues¹⁸⁴ performed a randomized, double-blind, placebo-controlled trial in 42 men with PD, comparing iontophoresis with verapamil to saline. Their results demonstrated similar measured curve reduction in both groups. In 2005, a prospective, randomized, placebo-controlled study compared the results of patients receiving iontophoresis with verapamil and dexamethasone versus 2% lidocaine. In the verapamil treatment group, the plaque volume decreased and mean measured erect penile curvature was reduced by up to 50%, as compared with no changes in the lidocaine group. The only side effect reported was temporary erythema at the electrode site.¹⁸⁵ The ICSM's guidelines state: "Several controlled trials had evidence of reduced deformity following iontophoresis treatment using verapamil and dexamethasone." Although larger trials remain to be done, current studies suggest that iontophoresis is nontoxic and noninvasive, potentially lending its most beneficial use to those with mild to moderate curvature or those with plaque-related pain.^{148,186–189}

Penile Traction Devices

The mechanisms through which mechanical strain can yield a biologic response have been studied in several nonpenile models, including bone, muscle, and Dupuytren scar. Research has shown that mechanical stress modulates cell function in a process called mechano-transduction by activating multiple signal transduction pathways via the internal cytoskeleton and extracellular matrix.¹⁹⁰ Histologically, tension has been demonstrated to reorient collagen fibrils parallel to the axis of stress.^{191,192} Genetically, mechanical shear stress has been shown to cause an upregulation of antifibrotic genes.¹⁹³ Levine¹⁹⁴ published the first pilot study on traction therapy in men with PD. Penile traction therapy was initiated with the Fast Size Penile Extender (Alison, Viejo, California) for a period of 6 months, 2 to 8 hours per day. Curvature was reduced in all men with a mean reduction of 22°, and the mean IIEF increased from 44.6 to 55.0 for the treatment group. Stretched penile length improved in all patients (100%), with an increase in length up to 2.5 cm. There was no change in penile sensation or new ED.¹⁹⁴ Gontero and colleagues¹⁹⁵ performed a study on traction therapy, evaluating its efficacy in change in curvature. Traction was performed using the Andropenis

(Andromedical, Madrid, Spain) penile extender for 6 months, 5 to 9 hours per day. After 6 months, penile curvature decreased in 6 patients from a mean baseline value of 31° to 27°. Curvature worsened in 1 patient and remained unchanged in 8 patients. Greenfield¹⁹⁶ performed a critical review of these 2 studies and suggested factors that may account for the different results, including the duration of disease, plaque calcification, and methodology of measuring curvature.¹⁹⁶ The ICSM's guidelines state: "Early evidence from two small non-controlled prospective trials have reported a reduction of deformity and increased penile length with traction therapy."¹⁴⁸ Although further large-scale trials are necessary, in regard to this relatively noninvasive, safe treatment option, the primary limitation of traction is that prolonged daily use is necessary to obtain a clinical benefit.

SUMMARY

Even though increased basic science research into the pathophysiology of PD has brought about new insights into the potential cause and treatment options for PD, an ideal, reliable, and effective nonsurgical therapy still eludes the practicing urologist. It is apparent from the review of the literature regarding medical options for the treatment of PD that we still lack controlled clinical trials with uniform standardized assessments and objective measures of deformity, including curvature and circumference. A key to elucidating the beneficial effects of various medical therapies lies in the standardized evaluation of patients with PD across various studies, allowing these proposed benefits to be confirmed and applied to all populations.¹⁹⁷ At this time, it seems that some combination of intralesional injection with traction therapy may provide a synergy between the chemical effects of the drugs and the mechanical effects of traction. Until a reliable medical treatment emerges, it does seem that currently available nonsurgical treatments can be used safely and may result in some reduction of deformity with improved sexual function. Because this is both a physically and psychologically devastating disorder for some patients, any degree of improvement in curvature and pliability of the erection, or even stabilization of the disease, with the goal of allowing comfortable intercourse for patients and their partners may be better than no treatment at all or surgery.

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Urodynamics

With a Focus on Appropriate Indications

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KEYWORDS

- Urodynamic • Uroflowmetry • Incontinence • Sphincter electromyography • Pressure-flow study
- Detrusor-sphincter dyssynergia

KEY POINTS

- Optimal use of urodynamic testing requires the formulation of urodynamic questions.
- The purpose of urodynamic testing is to supplement a patient's clinical history and physical examination with a series of tests that are designed to assess the storage and voiding phases of micturition using noninvasive and invasive methods.
- Appropriate ancillary staff training and patient preparation are essential to a successful urodynamic examination.

INTRODUCTION

Urodynamic testing has become a standard part of the available diagnostic armamentarium for the evaluation of patients with lower urinary tract dysfunction.¹ Optimal use of an urodynamic test requires the formulation of urodynamic questions, namely, "What is the information I need to obtain from the test?" and "What is the most appropriate urodynamic technique to obtain these results?"² An understanding of when to use certain urodynamic tests can be derived from the literature, from clinical practice guidelines, and from clinical experience.

URODYNAMIC TESTING IN CONTEXT

The purpose of urodynamic testing is to supplement a patient's clinical history and physical examination with a series of tests that are designed to assess the storage and voiding phases of micturition, using noninvasive and invasive methods. Observations seen during these tests and the clinician's interpretation can help identify potential bladder safety issues (eg, elevated bladder storage

pressures), help to guide treatment, predict outcomes, and correlate with patient quality of life.

Before performing a urodynamic test, a clinical evaluation should be completed to identify the relevant urodynamic questions. A thorough history is necessary to obtain a clear understanding of the patient's complaints, including type of symptoms (ie, urgency, frequency, urge incontinence, stress incontinence, pain, other voiding and storage symptoms), severity and duration of symptoms, both associated with the symptoms, previous therapies, and relevant medical comorbidities. A physical examination can identify specific findings (pelvic prolapse, urethral diverticulum, pelvic mass), which may contribute to or cause the symptoms of interest. Patients can also be asked to complete a voiding diary to assess objectively fluid intake, voided volumes, episodes of incontinence, and voiding frequency. Pad-weight testing helps quantify the amount of urine lost during incontinence episodes.³ Data from validated questionnaires help to quantify symptoms and their affect on quality of life.⁴⁻⁸ To be most useful, data obtained from a urodynamic test must be considered as supplemental to clinical data. For instance,

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identification of stress incontinence on a urodynamic test is of limited importance if the patient reports severe urge incontinence as the primary complaint.

OVERVIEW OF URODYNAMIC TESTING

Both noninvasive and invasive urodynamic techniques can be used to help qualify and quantify lower urinary tract activity during the micturition cycle. Noninvasive tests include uroflowmetry and postvoid residual (PVR). Invasive tests include cystometry, sphincter electromyography (EMG), videourodynamics (VUDs), pressure-flow study (PFS), and urethral function tests. An appropriately formulated urodynamic question might warrant one or more of these individual procedures to answer the question. We will begin with an overview of noninvasive urodynamic tests. We will then discuss invasive urodynamic tests, with separate sections devoted to the storage and voiding components of the micturition cycle.

Preparing the patient for invasive urodynamic testing can greatly affect usefulness and efficacy of the test. Patients generally tolerate urodynamic testing well, but feelings of anxiety, discomfort, and embarrassment are not rare.⁹ Studies of patient experiences with urodynamic testing indicate that more than 70% of patients would be willing to repeat invasive urodynamic testing if medically indicated^{9,10} and most thought the testing was the same or better than they expected it would be.^{11,12} As with all invasive procedures, informed consent should be obtained and all questions addressed.

It is the authors' practice to distribute standard patient instructions about urodynamics before the testing. These explain the testing procedures using nonmedical terminology, as well as the rationale for the testing. Patients are instructed to maintain their regular diet and to take their scheduled home medications. They are asked to arrive to the clinic with a full bladder to provide a urine specimen and possibly perform an initial noninvasive uroflow study. Poststudy instructions explain that they can resume routine activities and that they may experience mild dysuria, hematuria, and/or increased bladder sensitivity for 24 to 48 hours after the test.

All patients should undergo urinalysis to screen for signs of a urinary tract infection at the time of procedure. Patients with a symptomatic infection should have the urodynamic test deferred until the infection has been treated. Limited data exist regarding the usefulness of preprocedural antibiotic administration.^{11,12} The American Urological Association (AUA) *Best Practice Statement on*

Urologic Surgery Antimicrobial Prophylaxis states that antibiotic prophylaxis before urodynamic testing is indicated only in patients with risk factors, specified as advanced age, anatomic anomalies of the urinary tract, poor nutrition status, smoking, chronic corticosteroid use, immunodeficiency, externalized catheters, colonized material, coexistent infection, and recent prolonged hospitalization.¹¹ Recommended antibiotics include oral fluoroquinolones or trimethoprim-sulfamethoxazole; however, patient allergies, prior urine cultures, and local antibiogram patterns should be considered.

Patients with spinal cord injuries above T6 are at risk for experiencing autonomic dysreflexia (AD) during bladder filling, characterized by an acute increase in blood pressure and bradycardia, accompanied by symptoms such as headache, piloerection, skin pallor, profuse sweating, or skin flushing.¹³ Untreated AD can result in intracranial hemorrhage, retinal detachment, seizures, and death. A prior history or the risk for AD should be noted and appropriate preparations and/or precautions followed. Many patients know their typical triggers and these most often involve stimulation of the bowel or bladder.¹⁴ Preparations in the urodynamic test suite include monitoring blood pressure and heart rate throughout the study. If symptoms of AD are identified during urodynamic testing, the trigger (usually filling of the bladder or catheter placement) should be removed by draining the bladder and then removing catheters if needed. Additionally, the patient should be placed in reverse Trendelenburg (head up) to take advantage of any gravitational reduction in blood pressure and loosen any tight clothing or restrictive devices. If blood pressure elevation does not resolve, 1 to 2 inches of nitropaste can be applied to the chest and wiped off after blood pressure values normalize.¹³

As with all invasive procedures, certain patients may also experience vasovagal syncope during urodynamic testing. For this reason, some centers have a policy that all patients, male and female, perform the voiding phase of the study in the seated position. In contrast to treatment of AD, vasovagal syncope requires the patient be placed in the Trendelenburg position to increase blood flow to the head and/or chest.

Noninvasive Emptying Assessment

Uroflowmetry (uroflow) is a noninvasive method to measure the flow of urine during micturition. Patients are instructed to void with a comfortably full bladder. Measurements obtained during uroflow are peak flow rate (Qmax), average flow

rate, voiding time, voided volume, and flow pattern (eg, flat, bell-shaped curve, saw-tooth, intermittent). Voided volume must be equal to or greater than 150 mL for uroflowmetry results to be valid.^{15,16} A reduced flow rate suggests the presence of bladder outlet obstruction, reduced bladder contractility, or both. Because patients are not always able to complete the voiding phase of multichannel urodynamic testing, noninvasive uroflow can be a useful adjunct after the filling portion of a PFS has been completed.

PVR can be measured directly by draining the bladder with a catheter, or indirectly with bladder ultrasound or fluoroscopy (if radiopaque contrast has been instilled into the bladder before voiding). Bladder outlet obstruction can be due to many causes that can be suggested by clinical history, but cannot be diagnosed with just PVR testing.

Assessment of Bladder Storage Function

Simple cystometry is an inexpensive evaluation that can assess bladder sensation and detrusor behavior during filling. It can be performed in a regular examination suite in either the standing or supine position. The study requires a small sterile catheter (usually 12–14F) and a 60 mL catheter-tip syringe with the plunger removed. Room temperature sterile saline or water is used as the filling fluid. The catheter is inserted per urethra with sterile technique and PVR volume measured. The syringe is attached to the end of the catheter as a funnel. Using gravity, the fluid is gradually poured (approximately 50 mL/min increments) into the funnel to fill the bladder. As filling proceeds, the patient is asked to report their first sensation of bladder filling, normal desire to void, strong desire to void, and maximum bladder capacity.¹⁷ In the authors' practice, the scripted questions we ask our patients are (1) first sensation, "Tell me when you first feel any fluid or a coolness in your bladder;" (2) first desire to void, "If you're watching TV, tell me when you would go to the bathroom at the next commercial;" (3) strong desire to void, "Tell me when you can't wait for the next commercial;" and (4) maximum capacity, "Let me know when you can't hold any more in your bladder." Involuntary detrusor contractions can be seen by watching the meniscus in the syringe as a back-pressure against gravity. Care should be taken to correlate these observations with any patient movement. If indicated, a full bladder cough stress test can be performed after the catheter is removed.

Complex filling cystometrogram (CMG) allows for measurement of bladder pressure during filling. Single-channel recording of bladder pressure can

offer information about bladder sensation, capacity, compliance, and involuntary detrusor contractions.¹ The urodynamic catheter (6–10F) is placed into the bladder and room temperature fluid is instilled at 30 to 50 mL per minute. Bladder sensation (first sensation, normal desire, strong desire, and maximum capacity) is assessed. Studies in healthy volunteers indicate that these sensations are reproducible.¹⁷ Extremes in sensation likely represent a pathologic abnormality.

Commonly, disposable air-charged or water-filled urodynamic pressure-measurement catheters are used to perform cystometry. Air-charged catheters are newer in design; therefore, most prior research was based on water-filled systems. There are notable differences in how each catheter responds to changes transient and sustained pressures and they do not give interchangeable results.¹⁸ However, both catheter types are widely accepted for clinical use, and most observed differences are outside the range of what is generally relevant to urodynamic studies. Standard double- and triple-lumen catheters are available. Double-lumen catheters have one port for fluid inflow and a second port to measure vesical pressure (Pves). Triple-lumen catheters provide a third, more proximal, sensor port, which can be positioned at the level of the external urethral sphincter to measure bladder and urethral pressure simultaneously.

Multichannel urodynamic testing is the stepwise addition of a rectal catheter to a filling CMG, to measure abdominal pressure (Pabd). This allows the testing clinician to incorporate information about the relative contribution of Pabd changes (ie, with cough or Valsalva) to bladder behavior. Rectal catheters come in multiple styles, including fluid-filled rectal balloon and air-charged catheters. Both types of catheters are placed in the rectal vault, proximal to the anal sphincters. Presence of stool in the rectum can affect Pabd readings. In patients without a rectum, the catheter can be placed either in the vaginal vault or in a fecal stoma to allow measurement of the Pabd. Regardless of catheter system, the International Continence Society (ICS) recommends that all urodynamic catheters be zeroed to atmospheric pressure and reference height is set to the level of the upper edge of the pubic symphysis.¹⁶

In urodynamic terminology, Pves is the measure of the bladder pressure and Pabd is the abdominal pressure measured by the catheter in the rectum. Detrusor pressure (Pdet) is the difference of Pves minus Pabd. Calculation of Pdet is often important as a measure of detrusor muscle function in patients who are able to generate Pabd. Whereas the calculated Pdet represents the viscoelastic

properties and tone of the bladder wall, all three tracings (Pves, Pabd, and Pdet) should be evaluated when looking at a urodynamic study to monitor for artifacts and other factors contributing to the Pdet tracing.

Sphincter EMG is an indirect measure of pelvic floor and urethral sphincter muscle contractility.¹⁹ This is a measurement of depolarization of the sphincter muscle membrane. Urodynamic questions that can be answered include information about outlet contraction and relaxation in relation to the timing of other components of the urodynamic study. EMG is typically performed with surface patch electrodes, placed on the perineum. Needle electrodes EMG can be used but are more invasive and uncomfortable.

In a normal urodynamic study, the sphincter EMG has a baseline resting activity that may increase slightly as the bladder fills (guarding reflex). EMG activity will also increase with stress or Valsalva maneuvers. During the first phase of voiding, there should be cessation of activity as the urethral sphincter relaxes. If EMG activity increases with voiding, this may represent detrusor-sphincter dyssynergia (DSD), dysfunctional voiding, or normal attempts to prevent voiding in the presence of an involuntary detrusor contraction.²⁰ DSD is found in patients with suprasacral spinal cord lesions. As an example, a 58-year-old man with an incomplete C2/3 spinal

cord injury demonstrates a strong involuntary detrusor contraction, with DSD based on both increased intraluminal urethral pressure and increased sphincter EMG activity (**Fig. 1**).

VUDs, or fluorourodynamics, involve synchronous radiographic imaging of the bladder with multichannel urodynamic testing. It was originally (1970) called this because the information was recorded to videotape.²¹ Ultrasonography is an alternative imaging modality but not used widely. Fluoroscopy is used to offer dynamic images of the anatomy with maneuvers. Other pathologic findings can be visualized with these images, including vesicoureteral reflux, urinary tract stones, and bladder diverticula.

The use of fluoroscopy offers useful information in complex patients. For example, a 75-year-old man presented for evaluation of stress urinary incontinence, urinary frequency, and recurrent urinary tract infections (**Fig. 2**). He had a urologic history notable for a robotic-assisted laparoscopic radical prostatectomy for prostate cancer with concomitant bladder diverticulectomy 1 year before presentation. Postoperatively, he developed a bladder neck contracture that was dilated and he now performs obturation daily. Urodynamic evaluation showed first desire to void at 90 mL, strong urge at 121 mL, and capacity of 144 mL. Pdet rose from a baseline of 0 cm H₂O to 9 cm H₂O at a volume of 144 mL. Pves, on the

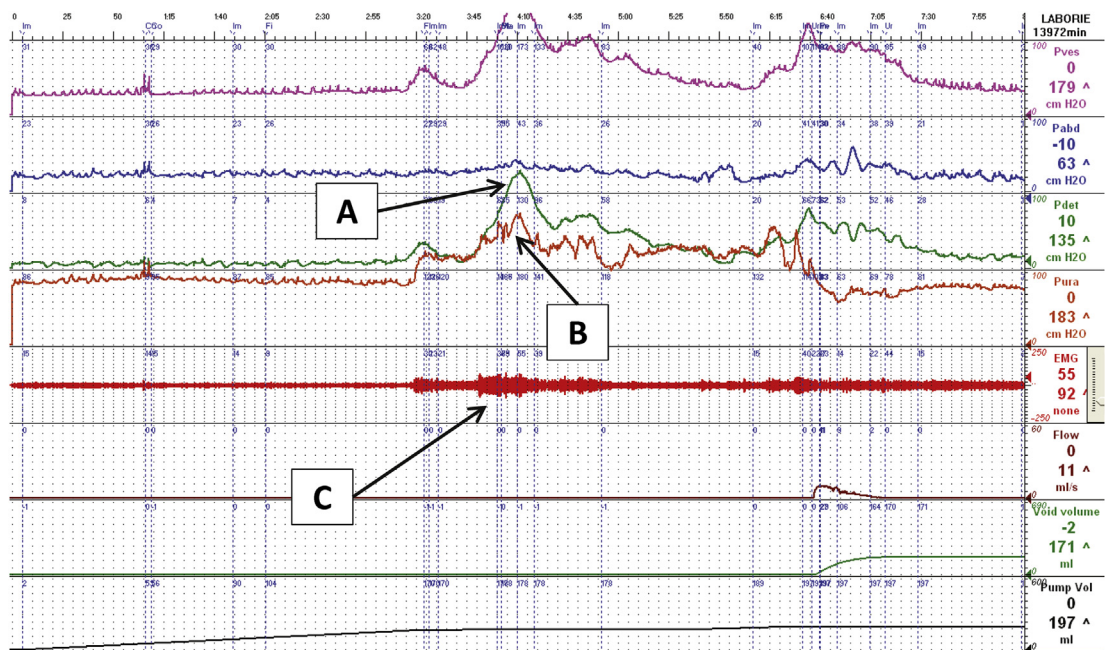


Fig. 1. (A) Strong voluntary detrusor contraction (Pdet) with (B) simultaneous increased external urethral sphincter contraction (Pura) and (C) increased EMG activity.

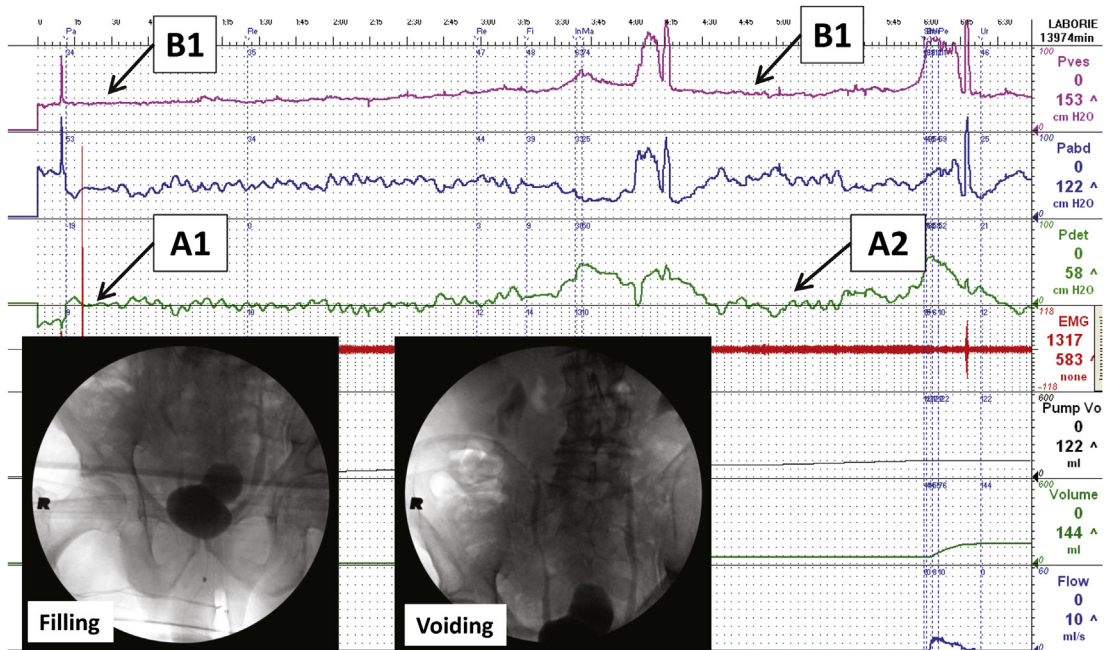


Fig. 2. Pabd has significant baseline variability. When trying to determine compliance, the baseline variability affects Pdet; therefore, there is not a notable change in compliance (A1 vs A2). However, Pves baseline is about 34 cm H₂O (B1) and increases to 48 cm H₂O (B2), for a change of 14 cm H₂O. Although this is not a clinically significant compliance change, the addition of fluoroscopy shows a diverticulum and bilateral vesicoureteral reflux (right grade II–V, left grade III–V). The diverticulum filled more and reflux increased bilaterally with voiding.

other hand, rose from a baseline of 34 cm H₂O to 48 cm H₂O at a volume of 144 mL. He had involuntary detrusor contractions at 90 mL and 122 mL, with incontinence. Overall, these findings suggest normal detrusor compliance, reduced bladder capacity, detrusor overactivity, and intrinsic sphincter deficiency. However, fluoroscopy demonstrated a bladder diverticulum and bilateral vesicoureteral reflux (grade II–V on the left side and grade III–V on the right side occurred at 33 mL with 0 cm H₂O and 70 mL with 3 cm H₂O, respectively). The diverticulum filled more and the reflux increased bilaterally with voiding. Because of the vesicoureteral reflux, comment cannot be made about the patient's true bladder compliance because there is no longer a closed pressure reservoir and the bladder pressure may appear falsely safe.²² Addition of fluoroscopy alters both interpretation and recommended treatment of this patient.

Although fluoroscopy is often useful, providers should limit the number of images that do not contribute to the diagnostic value of the study.^{23,24} For many urodynamic studies, the essential static images include one for each of the following stages of the urodynamic study: scout, filling phase low volume, Valsalva maneuver (dynamic) at approximately 200 mL (or lower in patients

with decreased capacity), dynamic images during incontinence, cystometric capacity, during voiding, and postvoid. Additional images without the catheter may be needed during voiding if the patient is unable to void with catheter in place.²³

Assessment of Urethral Function

Abdominal leak point pressure (ALPP) is defined by the ICS as the "intravesical pressure at which urine leakage occurs due to increased abdominal pressure in the absence of a detrusor contraction."¹ Lower ALPP values correspond to more severe stress urinary incontinence. The ALPP can be induced either by cough (cough leak point pressure) or by Valsalva maneuver (Valsalva leak point pressure). ALPP values can be used to quantify the severity of stress urinary incontinence, and this information can be used to guide treatment selection. The usefulness of urodynamics to evaluate incontinence is demonstrated with a case of a 36-year-old woman referred for evaluation of incontinence after repair of a urethral diverticulum. Office cystoscopy showed no evidence of persistent urethral diverticulum. The 24-hour pad weight testing was 248 g. Urodynamic testing showed severe intrinsic sphincter deficiency with urethral hypermobility (Fig. 3).

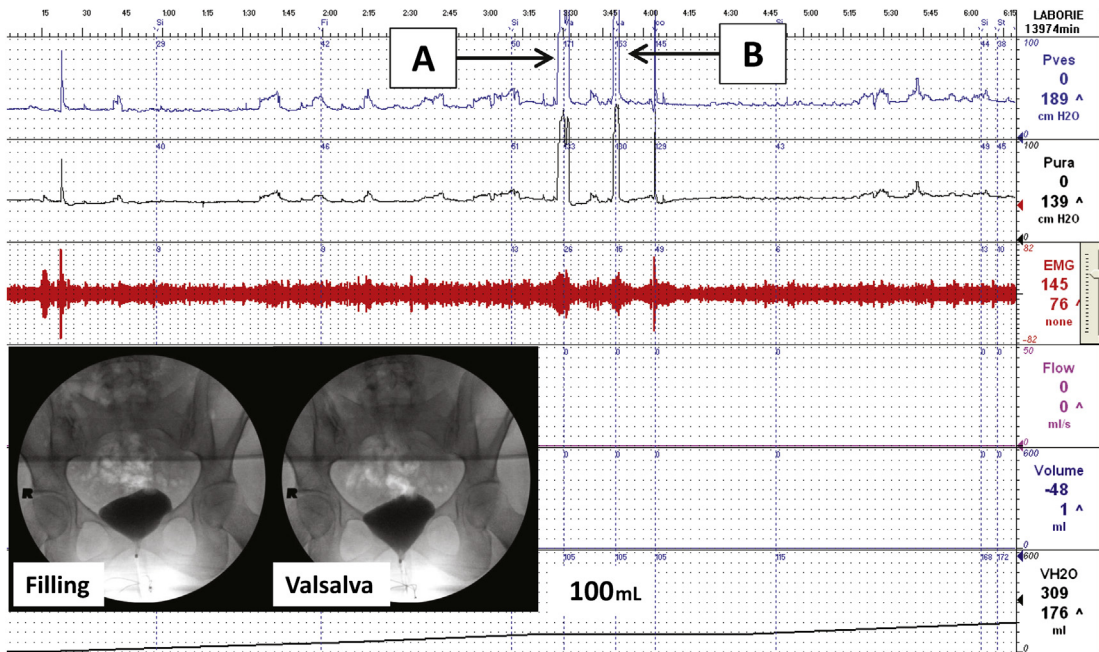


Fig. 3. (A) Valsalva leak point pressure and (B) cough leak point pressure (CLPP) assessed at 100 mL. Compensatory urethral pressure and EMG activity noted. Bladder neck was open with rest on fluoroscopy and urethral hypermobility with leakage was seen with Valsalva and cough.

Bladder volume can affect ALPP measurements. The testing was first performed at a bladder volume of 150 mL²⁵ and has since been performed at volumes of 200 to 300 mL.²⁶ Catheter size is another important consideration in the measurement of ALPP. A transurethral catheter can partially occlude the urethral lumen, potentially distorting the value of the ALPP.^{27,28} Although there is no standard catheter size recommended for urodynamic testing, it is generally agreed that smaller catheters have less occlusive potential and are usually preferred.

Urethral pressure measurements are used to assess urethral competence and incontinence severity. Although it is fully accepted that urethral pressure is an important and integral component to urinary continence, it remains challenging to measure and characterize this pressure in a reliable manner.²⁹ The urethral pressure profile (UPP), maximum urethral pressure, and maximum urethral closure pressure (MUCP) may be used as part of the urodynamic evaluation for stress urinary incontinence. UPP is the graph of intraluminal pressure that is produced when urethral pressure is measured by a catheter along the entire length of the urethra. The maximum urethral pressure is recorded on this graph and the maximum difference between the urethral pressure and the Pves is the MUCP,¹ which is the most commonly used measurement of the urethra in current practice. MUCP

has been assessed in multiple studies to determine whether it can be used to predict success among women undergoing anti-incontinence procedures, with mixed results.^{30,31}

Invasive Assessment of Bladder Emptying Function

A PFS involves the simultaneous measurement of Pves, Pabd, and voiding flow. Flow is recorded as a milliliter per second and Qmax is the highest flow rate recorded in the study. Urodynamic questions that can be answered include information about detrusor contractility and evidence of bladder outlet obstruction. Detrusor contractility and coordination with the external urethral sphincter and pelvic floor is assessed during the PFS by correlating Pdet increase with urethral pressure or EMG relaxation. As an example, a 46-year-old man with multiple sclerosis was evaluated for straining and double voiding. Office cystoscopy showed prostatic hypertrophy with concentric bladder neck narrowing. Multichannel urodynamic testing with fluoroscopy confirmed the presence of bladder outlet obstruction without any evidence of DSD (**Fig. 4**). The patient was offered a transurethral resection of the prostate rather than interventions to manage DSD.

There are several nomograms developed to help characterize the PFS in men. Perhaps the most

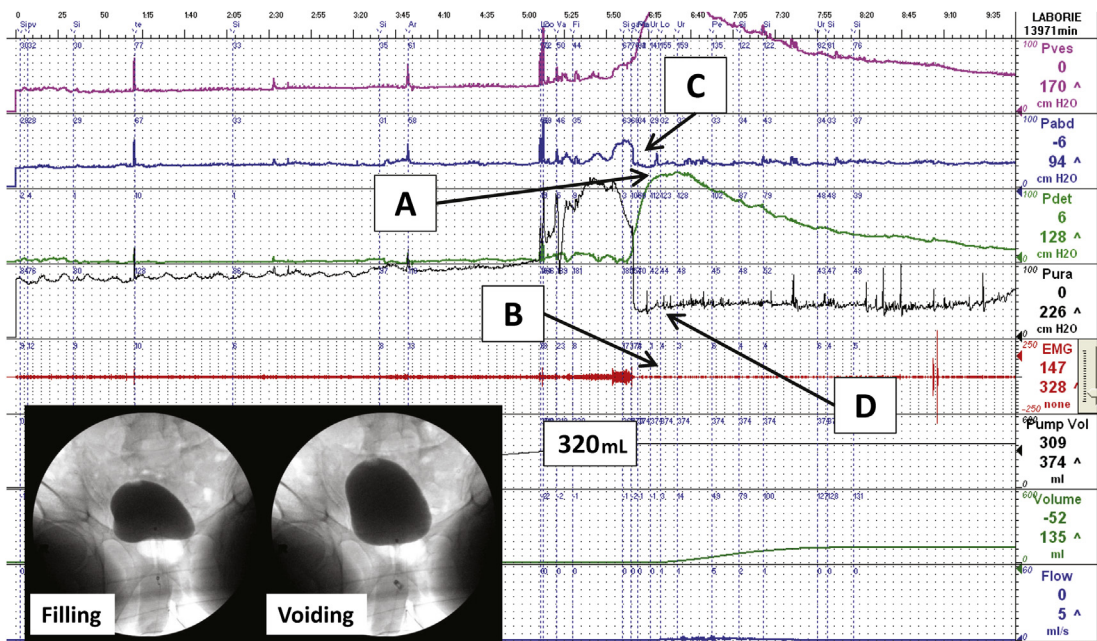


Fig. 4. (A) Voluntary detrusor contraction (Pdet) at 320 mL coincided with (B) decreased EMG activity and (C) no evidence of Valsalva voiding. Fluoroscopy showed the bladder neck did not open with voiding but (D) external urethral sphincter pressure (urethral pressure) did decrease. There was urine flow but with high voiding pressure (92 cm H₂O) and Qmax of 4 mL/sec.

widely used is the ICS nomogram for pressure flow analysis.³² This analysis represents a plot of Pdet versus urethral flow to provide characterization of the flow as obstructed, unobstructed, or equivocal. Several other nomograms have been developed such as CHEAD (in chessboard format)³³ and linPURR (linearized passive urethral resistance relation),³⁴ which can be used in a similar manner to quantify the degree of obstruction.

PITFALLS AND TROUBLE SHOOTING

Avoiding technical complications during urodynamic testing begins with an appropriately planned study and quality control measures. Once urodynamic questions and the appropriate tests have been chosen, the equipment must be set up and calibrated. In most urodynamic testing suites, there is a specially trained registered nurse, nurse practitioner, physician assistant, or medical assistant to facilitate the procedure. Although there are many team members needed to perform the study, it is the responsibility of the physician to ensure quality. An experienced provider with a good team is able to interpret the mechanical, physical, and psychosocial factors that affect urodynamic testing.

One of the first challenges encountered with urodynamic testing is placing the urodynamic

catheter, which is small and malleable. If unable to pass the urodynamic catheter into the bladder, the urodynamic catheter can be piggybacked off a stiffer catheter, usually a coudé tip. Once the urodynamic catheter is in the bladder, the larger catheter is pulled out.

If that technique proves unsuccessful, urodynamic information can be obtained from a larger or more rigid catheter such as a red-rubber, Foley, or Mentor catheter. Pves can be transduced via one of these single-channel catheters with some modifications. First, after placement of the catheter, a Christmas-tree adaptor is placed into the catheter for attachment of a Y-connector (Fig. 5). The water-charged pressure system is in a direct line with the catheter and the infusion line must go in the side-port.

Because of significant flow turbulence that will be detected with the infusion line and pressure system in direct communication, Pves measurements can only be made when infusion is stopped (Fig. 6). It is the authors' practice to fill with a maximum of 30 mL per minute and stop infusion to check Pves every 50 mL volume. Pves measurements and calculation of compliance can be made along the tracing.

Routine cough and Valsalva maneuvers can also be tested (Fig. 7). Involuntary detrusor contraction will result in a rise in the vibratory tracing and

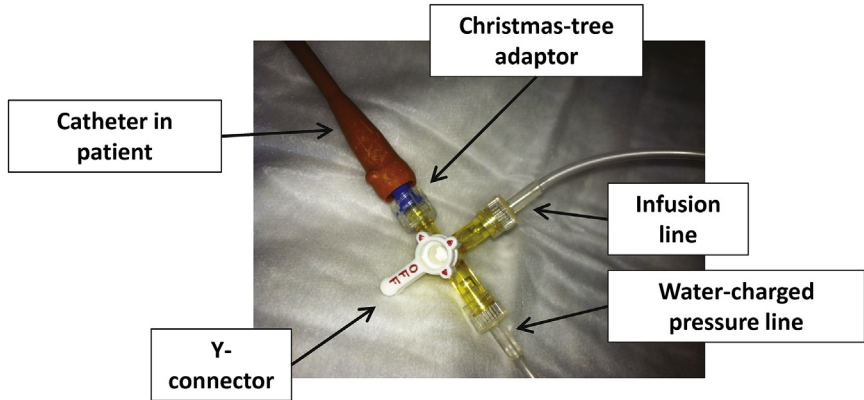


Fig. 5. Set-up for single-channel water-charged pressure monitoring.

infusion should stop to monitor contraction, as with any urodynamic study. Fluoroscopy can be used to augment anatomic evaluation. A PFS cannot be performed with this system but the catheter could be removed and uroflow performed.

ICS criteria for quality control include the following parameters: (1) ensuring that resting values for abdominal, vesical, and Pdet are all in a typical range, indicating they are not influenced by artifact; (2) confirming that abdominal and vesical pressures reflect live signal changes with talking or breathing, but that these variations do not appear in the Pdet tracing; and (3) checking that there is an equal response of abdominal and vesical pressures with a cough every 1 minute (or 50 mL) and before voiding.¹⁶ It is the authors' practice to check coordination of Pabd and Pves with a cough approximately every 200 mL if patient has a

normal to large capacity bladder (Fig. 8). This routine measurement allows accurate differentiation of detrusor forces acting on the bladder versus abdominal forces, as well as timely identification of artifacts.

There are several common problems encountered with urodynamic testing. These can be categorized as mechanical versus patient-related events (Table 1). Rapid identification and correction should be taken at the time of the study to maximize the usefulness of the study and to prevent incorrect data interpretation.

Mechanical events include a displaced catheter, expelled catheter, and EMG signal artifacts. Displaced tubes do not provide correct values if the sensor tip is against the rectal or bladder wall. Generally, the displaced catheter will not respond to quality control measures with the same

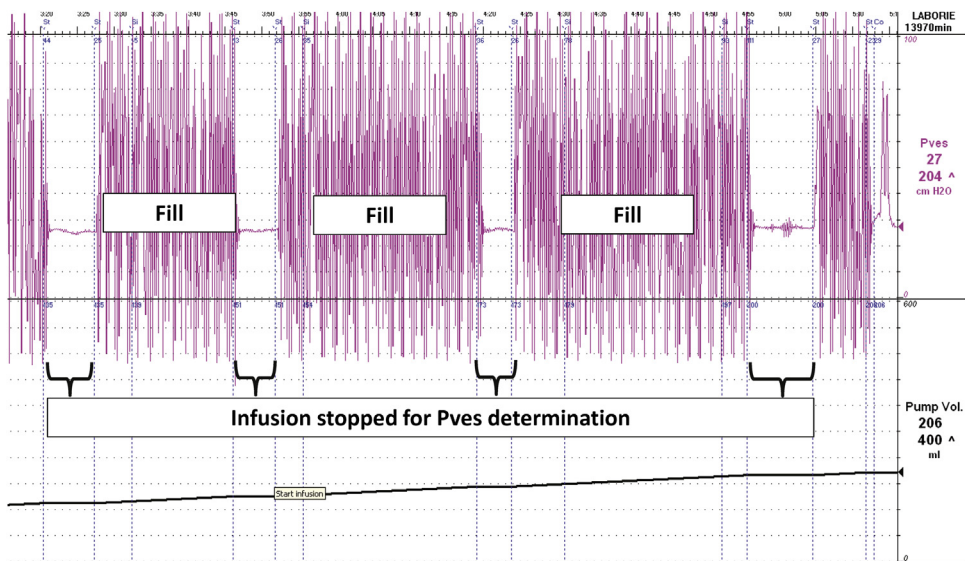


Fig. 6. Example of Pves tracing during single-channel fluid infusion and pressure check every 50 mL.

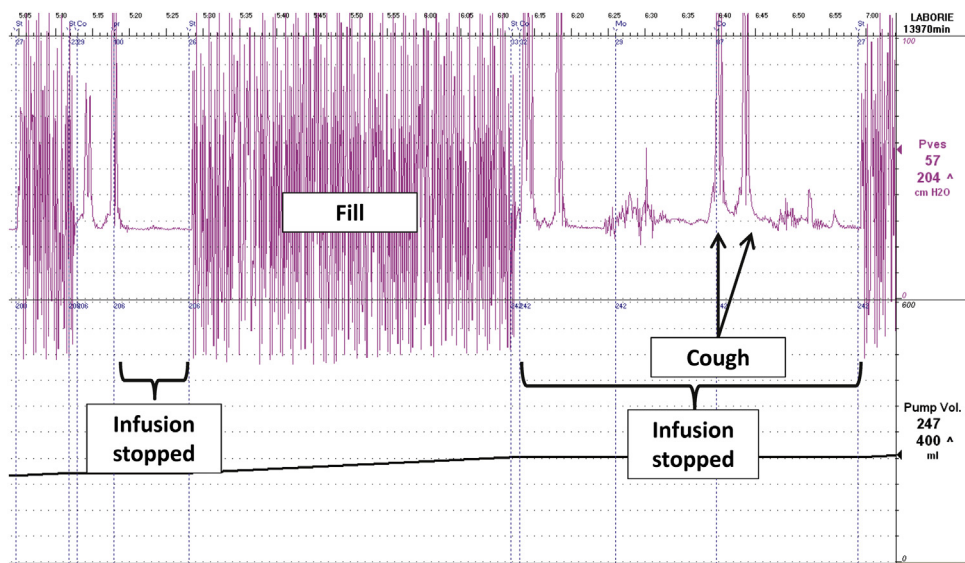


Fig. 7. Example of Pves tracing with cough and Valsalva during single-channel fluid infusion. Compliance can be determined from the Pves when not filling.

amplitude and, therefore, it should be repositioned. Prolonged rise or decrease in Pabd or Pves that does not respond symmetrically to a quality control measure (eg, coughing) can also be assumed to be a displaced tube. Expelled tubes will result in a negative reading for that tracing.

EMG signals are susceptible to artifacts created by electrical potentials that are not generated by those muscles targeted for assessment. Electrical equipment in the room might produce artifacts. A more contemporary source of tracing artifacts is

an implantable sacral neuromodulation device that will give constant background amplitude tracing (**Fig. 9**). To avoid interference, the device can be turned off during testing. Lead placement in a poor location, over-thick hair, or wet skin will also interfere with EMG readings.

There are also technology-related artifacts that are dependent on the type of equipment used. For example, microtransducer sensors will detect urethral pressure differently according to orientation. Staff should be familiar with such equipment

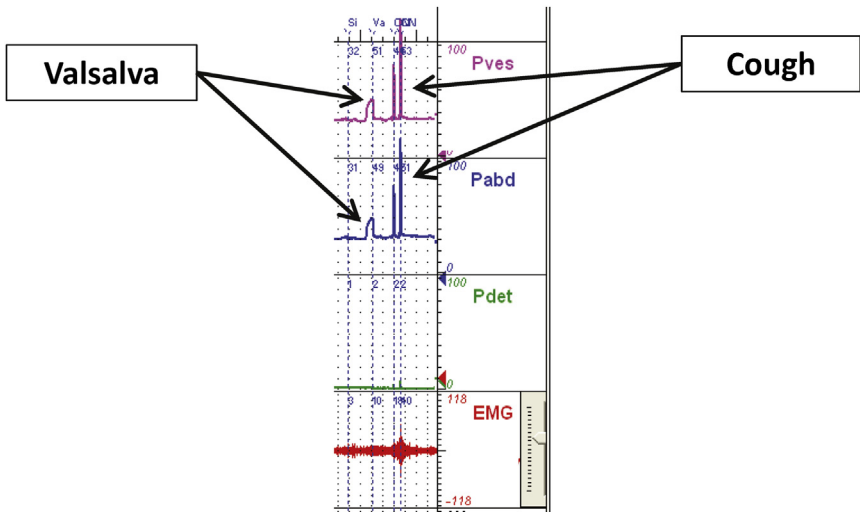


Fig. 8. Example of Valsalva and cough maneuvers to assess appropriate tracing response. Both Pabd and Pves respond with the same magnitude and timing, indicating an appropriate tracing. The calculated Pdet does not show a change in pressure. There is a compensatory EMG contraction.

Table 1 Pitfalls and troubleshooting in urodynamic testing		
Mechanical Events or Technical Pitfalls	Observed With	Problem Solving or Remedial Action
Displaced catheter	Poor correlation between Pabd and Pves Sometimes a slowly moving rectal catheter will suggest low bladder wall compliance	Reposition catheter and secure it
Expelled catheter	Abrupt negative value in Pabd or Pves	Replace catheter and secure it
Poor pressure transmission or spikes are of unequal height	Pabd, Pves	Reposition catheter to move away from interference (eg, bladder wall, rectal wall) Flush lines and ensure no air-bubbles
Poor EMG signal	Low-amplitude EMG tracing	Improve contact by removing hair or covering dry patch electrode leads with tape to prevent interference Reposition closer to sphincter
Neuromodulation device	Abundant persistent EMG signal artifact	Turn-off neuromodulation device or disregard EMG tracing
Fluoroscopy does not show bladder neck, urethra, or other anatomy	Fluoroscopic images	Reposition fluoroscopic arm
Patient-Related Events	Observed With	Problem Solving or Remedial Action
Rectal contractions and passing flatus	Fluctuating Pabd or negative tracing	Observe real-time and note on event log Consider during interpretation
Patient movement	Changing Pabd, Pves, EMG that correlate with patient movement	Observe real-time and note on event log Consider during interpretation
Symptom not reproduced	—	Eliminate barriers to study by reducing patient anxiety Mimic physiologic triggers Change position Remove urethral catheter if assessing voiding phase

parameters when administering and interpreting the test. As noted above, water-charged catheters require careful attention to the tubing position and water bubbles in the line to maintain stable pressure measurements. However, both water-charged and air-charged catheters, need careful calibration and zeroing.

Patient-related events can affect all aspects of the urodynamic study. To begin with, the patient may not be able to communicate their sensations, even if they can feel them. Urodynamic testing is an interactive procedure, in which feedback about sensations and discomfort is solicited from the patient. Although urodynamic testing can be

performed on patients without the ability to communicate, some information is lost.

Artifacts in Pabd can be caused by rectal spasms, contractions, and flatus. For example, a 51-year-old man was being evaluated for lower urinary tract symptoms after a prostate procedure (Fig. 10). The Pves tracing showed a significant amount of activity, which is only clarified by looking at Pabd, which had mirrored values. In this case, Pdet still gave a good tracing, allowing for accurate assessment of bladder pressure. This indicates the usefulness of the rectal catheter. Conversely, in a 67-year-old woman being evaluated for mixed urinary incontinence, the Pabd

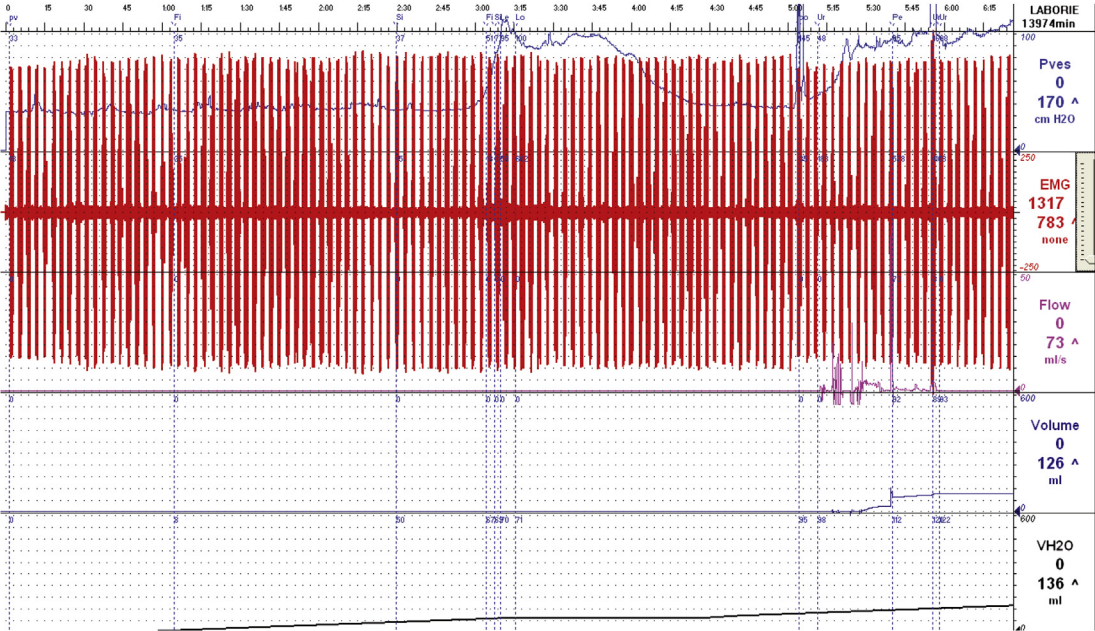


Fig. 9. EMG tracing artifact (red) due to sacral neuromodulation device.

was also not stable, but this affected the interpretation of Pdet. In this case, Pves provided a more useful and interpretable tracing to answer whether this patient had detrusor overactivity with filling (Fig. 11).

For fluoroscopic imaging, the position of the bladder may look lower and images of the urethra and/or bladder neck may be obstructed if the radiographic angle is straight in the anterior-posterior position. Repositioning the C-arm slightly

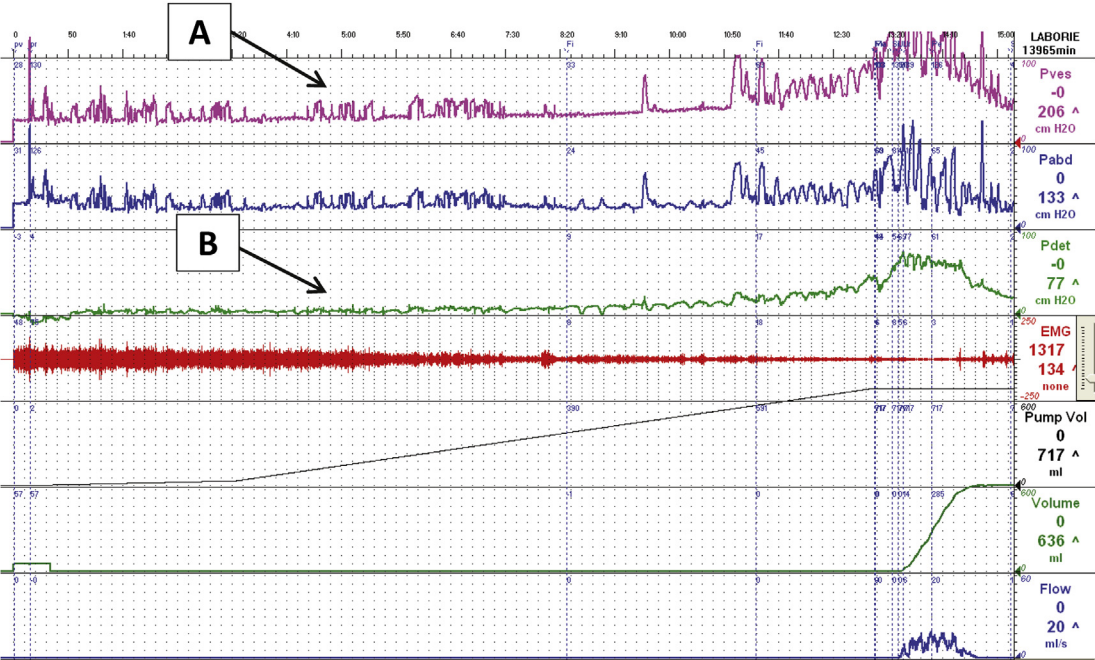


Fig. 10. (A) Pves tracing showed a significant amount of activity, which is only clarified by looking at Pabd, which had mirrored values. (B) Pdet is the accurate assessment of bladder pressure.

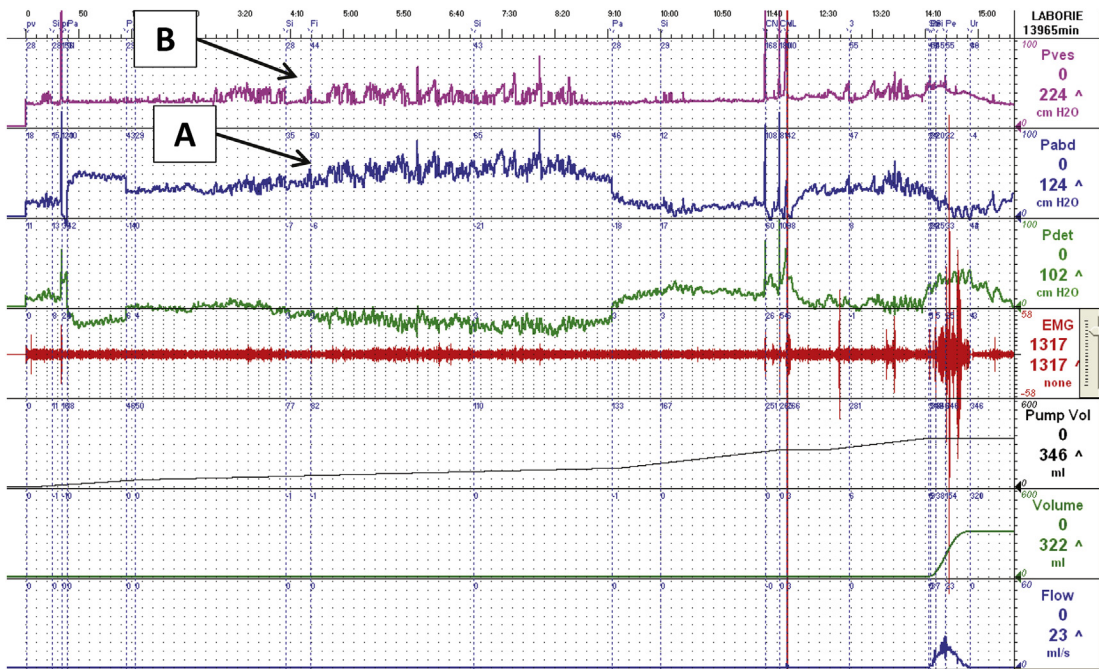


Fig. 11. (A) Pabd was not stable but, in this example, the artifact affected the interpretation of Pdet. Therefore, (B) Pves provided a more useful and interpretable tracing.

oblique allows these anatomic structures to appear. Similarly, in patients with urinary diversions and other potential pathological conditions, maneuvering the fluoroscopy source or the patient is required to delineate the anatomy.

The final pitfalls of urodynamic testing are that the study may not provide an answer regarding the posed urodynamic question, may give a false answer, or the study may not reproduce the patient's symptoms. If the testing does not reproduce clinical symptoms, some maneuvers can assist in eliciting these symptoms. To help with anxiety-related artifacts when asking the patient to void, leaving the room, or turning on the faucet is useful. Patient-reported triggers for urinary urgency (change in position, turning on the faucet or putting a hand in water) can be performed to illicit detrusor overactivity. Pelvic organ prolapse can be reduced to check for possible bladder function after a prolapse repair. Finally, the study can be repeated, "if the initial test suggests an abnormality, leaves the cause of troublesome lower urinary tract symptoms unresolved, or if there are technical problems preventing proper analysis."¹⁶

SUMMARY

As widespread access to urodynamic testing increases, appropriate clinical indications must be followed to minimize the possibility of unnecessary

testing, which can result in patient morbidity and extra expense. Current urodynamic guidelines² provide clinical parameters for some aspects of testing, but the nuances of urodynamic testing are largely in the hands of the practicing urologists to perform tests that will add to diagnosis, prognosis, and surgical planning.

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Vasectomy

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KEYWORDS

- Vasectomy • Sterilization • No-scalpel vasectomy • Minimally invasive vasectomy • Contraception
- Fascial interposition • Recanalization • Postvasectomy semen analysis

KEY POINTS

- Vasectomy is fast, safe, effective, and underutilized in comparison with tubal ligation.
- The preoperative visit is crucial for educating the patient on the risks and expectations of vasectomy, and especially that vasectomy is considered permanent.
- Minimally invasive vasectomy or no-scalpel vasectomy is preferable to conventional vasectomy.
- Fascial interposition decreases recanalization rates.
- Mucosal cautery appears to have the lowest vasectomy failure rates (<1%), although more high-quality comparative studies are needed.
- Patients must understand that an alternative birth-control method is necessary after the procedure until a postvasectomy semen analysis shows azoospermia.

INTRODUCTION

Vasectomy was first attempted on a canine in the 1800s, and has grown to be the most common operation performed by urologists today in the United States. More than 75% of vasectomies in the United States are performed by urologists. Vasectomy is a safe and effective form of contraception, yet it is underutilized today. Data collected in 2002 revealed that only 5.7% of United States men aged 15 to 44 years used vasectomy as a means of contraception.¹ Couples more commonly used condoms, oral contraceptives, or tubal ligation. Vasectomy is one of the most cost-effective contraceptive methods overall, its cost being similar to that of the Mirena Intrauterine System (\$844), the ParaGard Intrauterine Device (\$718), and the Implanon implant (\$791). The cost of vasectomy is one-quarter that of tubal ligation (\$707 vs \$2833).^{2,3} Compared with tubal ligation, vasectomy is equally effective in preventing pregnancy; however, vasectomy is less invasive, simpler, safer, faster, and less expensive. The benefits of

vasectomy over tubal ligation include faster recovery and return to work, local rather than general anesthesia, and ability to perform the procedure in the office rather than in the operating suite. Complications are rare for both procedures, but tend to be more serious for tubal ligation because it is more invasive.⁴

Although the advantages of vasectomy over tubal ligation are evident, tubal ligation is 2 to 3 times more prevalent in the United States. This discrepancy is present worldwide, but there are at least 10 countries where the prevalence of vasectomy equals or exceeds tubal ligation: Canada, Bhutan, United Kingdom, New Zealand, Netherlands, Spain, Republic of Korea, Malta, Tajikistan, and Denmark.⁵ The patterns of prevalence among the two groups in the United States have been found to be different. Tubal ligation is more prevalent among those with lower income and education levels, and among minority groups, whereas vasectomy use is higher among those with higher education and income and among white men.⁶

Disclosures: None.

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It is clear that vasectomy should be performed equally as or more frequently than tubal ligation, and couples should therefore be counseled about the pros and cons of various contraception options so that an informed decision can be made.

PREOPERATIVE EVALUATION

It is recommended that a face-to-face consult take place with the patient before planning the vasectomy. It is beneficial for the patient's partner to be present, although this is not required. An appropriate medical history should be taken, focusing on his reproductive history. Patients should also be questioned about bleeding tendencies and anticoagulant use as per routine preoperative workup. If there is suspicion of coagulopathy, coagulation tests may be necessary; otherwise, preoperative blood work is not needed. A physical examination of the scrotum should be performed, with emphasis on manually isolating the vas deferens, as well looking for scrotal abnormality such as undescended testis or testis tumors. If the patient is unable to tolerate this examination while isolating the vas deferens, he may not be a good candidate for local anesthesia. The preoperative examination may also alert the physician to patients whose vasa are difficult to locate or isolate; this allows planning of oral sedation or general anesthesia at the time of procedure if necessary.

Preoperative counseling of the patient is extremely important, and may prevent postoperative patient dissatisfaction or even litigation in the case of complications or vasectomy failure. Most patients have decided on vasectomy as their choice of permanent contraception before meeting with the physician, but a discussion of the risks, benefits, alternatives, and expectations should be conducted at the initial consultation. Patients should be counseled that vasectomy is considered irreversible and permanent. If the patient indicates any uncertainty regarding the desire for future fertility (eg, asking about sperm cryopreservation), vasectomy should not be performed and other contraceptive methods should be discussed. Likewise, if the patient seems too young and has not had children, it is reasonable to encourage other contraceptive options that are less permanent. The other benefit of the preoperative consult is to give the patient a "cool-down" period while waiting for the procedure date, thus allowing time for patients to change their mind if an impetuous decision for vasectomy has been made initially.

The following points should be addressed at the preoperative visit, many of which are addressed in more detail in this article.

- Alternatives to vasectomy
- Risk of infection or hematoma (1%–2%)
- Risk of chronic scrotal pain (1%–3%)
- Refrain from ejaculation for 1 week after the procedure
- Vasectomy is considered permanent
- Vasectomy does not produce immediate sterility; another form of contraception is required after the procedure until vasectomy success is confirmed by semen analysis
- Early vasectomy failure: risk of needing repeat vasectomy (<1%)
- Late vasectomy failure: after vasectomy success is confirmed by semen analysis, there is still a small chance of pregnancy (approximately 1 in 2000)

ANESTHETIC TECHNIQUE

Vasectomy can be performed under any type of anesthesia, but most are performed under local anesthesia because it is well tolerated with minimal morbidity. Certain patients may require intravenous sedation or general anesthesia if they cannot tolerate the procedure or if the vas is particularly difficult to isolate. Oral sedation in the form of a benzodiazepine (eg, diazepam) is offered by some clinicians to decrease anxiety and aid in relaxing the patient. Lidocaine or bupivacaine without epinephrine are typically the local anesthetic agent of choice, and are injected using a small needle (eg, 25 gauge or smaller) to reduce patient discomfort. Some clinicians apply an anesthetic cream to the skin before the needle stick, although it is unclear whether this significantly decreases pain.^{7,8}

VAS ISOLATION

Vasectomy is performed in 2 distinct steps: delivering and exposing the vas deferens out of the scrotum (vas isolation), and occluding the vas. Before the introduction of the no-scalpel technique, vas isolation was performed using the conventional technique, which used a larger incision and involved more dissection without special instruments. The no-scalpel vasectomy was first described in China in 1974.⁹ The no-scalpel technique has been found to have shorter operative times and to decrease the rate of hematomas, infections, and pain during the procedure.^{10–12} Today the standard of care is to perform a no-scalpel technique or a variation of such that remains minimally invasive.

In this article the term "minimally invasive vasectomy" is used to describe any vasectomy performed using a variation of the true no-scalpel

vasectomy originally described by Li Shunqiang, as long as it maintains a small skin opening and limits the amount of dissection around the vas with specialized vasectomy instruments. **Box 1** lists the exact steps of the original no-scalpel vasectomy.¹³ A more detailed description of the no-scalpel technique can be found in EngenderHealth's illustrated guide for surgeons.¹⁴ Note that the no-scalpel technique refers to vas isolation only and does not denote a method of vas occlusion. Two instruments were designed for this procedure: the vas deferens fixation ring clamp (**Fig. 1**), used to grasp the vas, and the vas dissector (**Fig. 2**), which is a sharp, curved mosquito hemostat without serrations. These instruments are widely used today for minimally invasive vasectomies.

Routine preoperative antibiotics are not necessary when performing minimally invasive vasectomy with the sterile technique. Scrotal skin

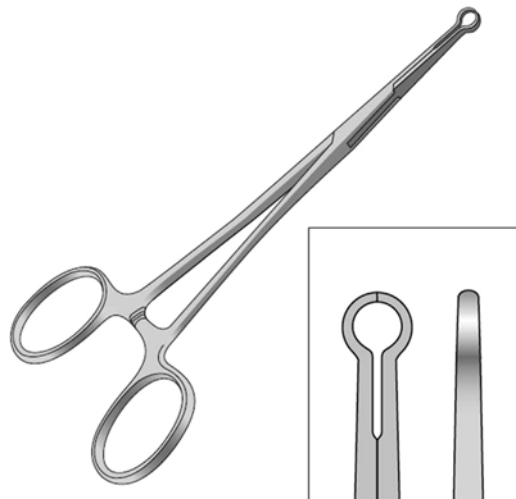


Fig. 1. Vas deferens ring fixation clamp. (© 2003 EngenderHealth. Used with permission.)

Box 1

Dr Li Shunqiang's no-scalpel vasectomy steps

- Isolate the vas manually to a superficial position under the median raphe
- Create skin wheal with local anesthetic and inject into perivascular sheath
- Use vas ring clamp to firmly secure the vas through the skin
- With vas dissector at 45° angle to the vas, puncture the skin, vas sheath, and vas wall with the left tip of the vas dissector, then remove
- Close the vas dissector and puncture the skin and vas sheath. Spread to make small opening in the skin, exposing the bare anterior wall of the vas
- Puncture the vas with one tip of the vas dissector
- Use supination motion to deliver a loop of vas above the skin opening while simultaneously releasing the vas ring clamp with the other hand
- Regrasp the vas with the vas ring clamp. Use vas dissector to gently strip the sheath and vasal vessels away from the vas, yielding a clean segment of vas
- Divide the vas, with or without excision of a vas segment, and occlude the lumen per physician's preference
- Via same puncture hole, fix opposite vas in ring clamp and repeat steps
- Leave puncture hole unsutured except in rare cases requiring closure

should be shaved, and the patient prepped with antimicrobial solution and draped in a standard sterile fashion. The procedure may be noticeably easier if the Dartos smooth muscle is relaxed, so using warm preparation solution and avoiding cold room temperatures may be beneficial.

Begin by isolating the straight portion of the vas with one hand using the 3-finger technique. Separate the vas from the spermatic-cord contents, and trap the vas over the middle finger and under the index finger and thumb (**Fig. 3**). There is no clear advantage of using one midline incision rather than bilateral incisions, and this should be decided upon based on surgeon preference and comfort. The bilateral incision approach may decrease the chance of cutting the same vas

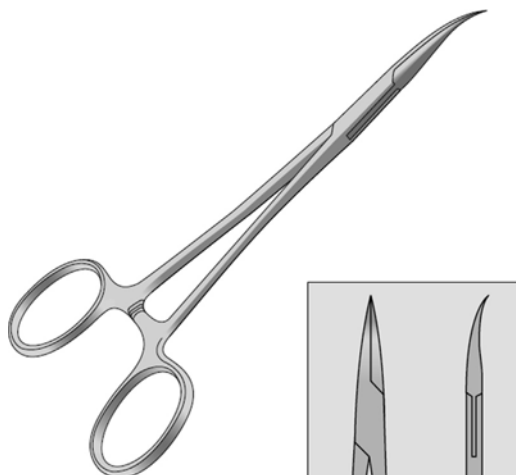


Fig. 2. Vas deferens dissector. (© 2003 EngenderHealth. Used with permission.)

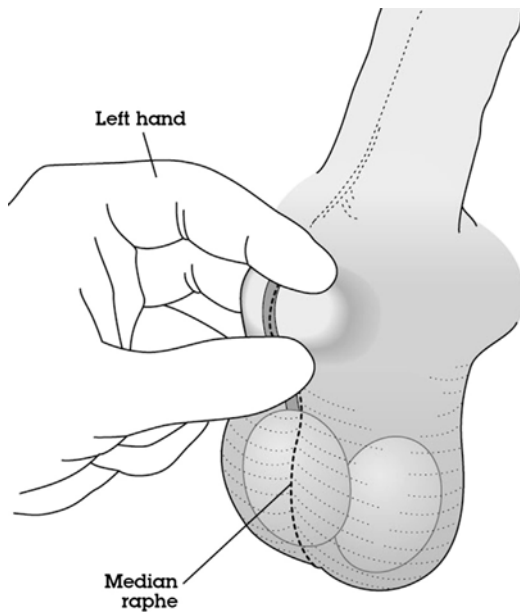


Fig. 3. Three-finger technique of vas deferens isolation. (© 2003 EngenderHealth. Used with permission.)

twice, although pulling on each vas should raise the testis on that side, which should eliminate this risk. Once the vas is isolated just underneath the skin between the fingers, local anesthetic is injected superficially to create a skin wheal. Injection into the vasal sheath can also facilitate anesthesia for the patient.

The next step of a minimally invasive vasectomy depends on whether an open-access or closed-access technique is performed. The closed-access technique, first described with the no-scalpel vasectomy, is performed by grasping the vas and the skin together with the ring clamp. As outlined in [Box 1](#), an opening is then made in the skin using the vas dissector to expose the vas. The vas is then skewered with one tip of the vas dissector and rotated to bring a vas loop out of the skin opening, and the bare vas is regrasped with the vas clamp. The vas dissector is spread apart to strip the vas ([Fig. 4](#)). Bleeding is often encountered at this step, which should be addressed immediately with cautery. Once an adequate loop of bare vas is outside the scrotum, it is then divided and occluded.

When using the open-access technique, the skin opening is made with the vas dissector first, allowing the vas clamp through the opening to grasp the vas, which is brought out of the skin opening. Further dissection of the perivasal tissues to expose the bare vas is performed with the vas dissector. To facilitate this, a longitudinal incision

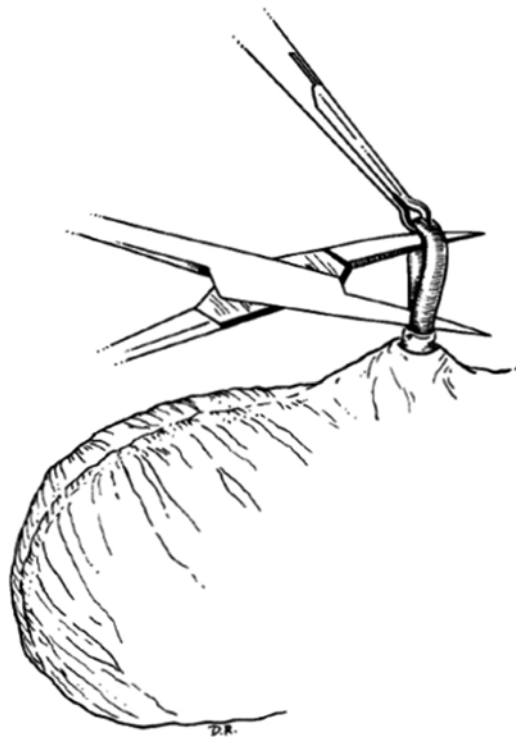


Fig. 4. The vas dissector is spread open, which brings the loop of vas deferens out of the scrotum and strips it of its sheath. (From Li SQ, Goldstein M, Zhu J, et al. The no-scalpel vasectomy. *J Urol* 1991;145:343; with permission.)

with a scalpel can be made through the vasal sheath along the vas, allowing the sheath to be separated from the vas more easily. Once a loop of bare vas is created, the remainder of the procedure is identical. The open-access technique was found in one study have a shorter operative time than the standard no-scalpel vasectomy, with no difference in length of incision.¹⁵

VAS DIVISION

Once a loop of bare vas deferens is outside of the wound, it is then divided with scissors. With a traditional vasectomy, a segment of vas is then excised. Questions of how much vas to remove and whether excision is even necessary remain unanswered. The optimal length of vas to excise, if any, should be left up to the surgeon. Excising a long (>2 cm) segment of vas may decrease the chance of recanalization,¹⁶ but will also require more dissection along the spermatic cord, increase complications, and make vasectomy reversal more challenging and less successful.¹⁷ The authors believe that if a segment of vas is excised, it should not exceed 1 to 2 cm in length.

As discussed later, the method of occlusion of the vas is more important for vasectomy success than is excision of a long vasal segment.

If a segment of vas is excised, sending the excised segments for histologic examination is not necessary. The measure of vasectomy success is determined by the results of the postvasectomy semen analysis (PVSA) rather than confirming vasal tissue on histologic evaluation. Despite this, some surgeons continue this practice because they find it useful to confirm vasal excision, and also out of fear of litigation in the case of a postvasectomy pregnancy.

VAS OCCLUSION

Vasectomy success can be measured by either azoospermia on PVSA or absence of pregnancy after vasectomy. In terms of achieving vasectomy success, the most important step comes after division of the vas and occlusion of the vas. There are several vas-occlusion techniques, including intraluminal cautery of one or both ends, ligation with suture, occlusion with clips, fascial interposition, and any combination of these. Review of the literature reveals many studies examining each of these techniques, yet it is difficult to conclude which occlusion method is superior, owing to study flaws and lack of uniformity in terms of patient follow-up and measurement of success. Several methods of vas occlusion are presented here, and their efficacy discussed.

Intraluminal cautery, or mucosal cautery, is performed by applying thermal cautery or low-voltage electrical cautery with a needle tip within the lumen of the vas. It is unclear as to what length of cauterized mucosa is required to create occlusion, but most surgeons cauterize between 5 and 15 mm of vas lumen. The goal is to destroy only the mucosal layer, which then scars to create a plug in the lumen. Avoiding thermal injury to the muscular layer prevents complete sloughing of the cauterized vas segment, which could potentially allow recanalization. When mucosal cautery is applied to both the abdominal and testicular ends of the divided vas deferens without using

fascial interposition, vasectomy failure rates are less than 1%.^{18–20}

Fascial interposition has become a commonly used technique, because when used with other methods of occlusion it decreases vasectomy failure rates.²¹ The goal is to separate the two newly divided ends of the vas to reduce the chance of recanalization. To do so, a layer of vas sheath is placed between the two ends of the vas as a tissue barrier with the help of 1 or 2 absorbable sutures (Fig. 5). The fascial layer can be placed over the abdominal or the testicular end. When fascial interposition is combined with mucosal cautery of both ends of the divided vas, failure rates are less than 1%.^{20,22–26}

Another commonly used method of vas occlusion is suture ligation of the vas. Studies evaluating vasectomy using ligation of the vas without fascial interposition reveal a wide range of failure rates from 0% to 12.7%.^{21,27–33} The only randomized study reported a failure rate of 12.7% out of 416 patients who received vasectomy and were followed up postoperatively.²¹ A high-quality prospective study revealed a failure rate of 11.5%.³³ Because of the higher rates of failure, ligation of the vas without fascial interposition is not recommended.

Combining fascial interposition with the suture ligation technique improves success rates, as proved in a randomized study in which fascial interposition decreased the failure rate by half, down to 5.8%.²¹ Other studies showed better outcomes. A retrospective review of 2150 patients undergoing suture ligation and excision with fascial interposition had no failures.³⁴ More recently, a large prospective study from Iran reported a 2.1% failure rate.³⁵ Although fascial interposition increases efficacy when combined with suture ligation, failure rates are often unacceptably high.

In 2002, 29.5% of United States physicians reported using clips as part of their occlusion technique.³⁶ Similar to ligation with suture, applying clips to the vas without using fascial interposition may result in undesirable rates of vasectomy failure. One study revealed a failure rate of 8.7%,³⁷ whereas smaller older studies report failure rates

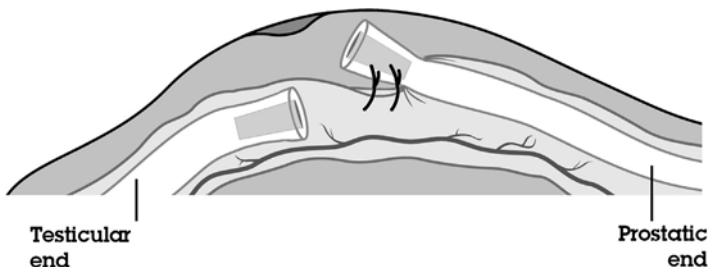


Fig. 5. Fascial interposition is performed by suturing a layer of vas sheath between the two ends of the vas deferens, which separates the ends of the vas and decreases the risk of recanalization. (© 2003 EngenderHealth. Used with permission.)

of less than 1%.^{38,39} There are limited data assessing the efficacy of vasectomy when fascial interposition is used in conjunction with clipping the vas. The only study found reported no failures out of 1073 patients.⁴⁰ There is therefore insufficient evidence to determine the exact efficacy of using clips, but fascial interposition is likely to decrease failure rates based on the randomized study of fascial interposition and suture ligation.²¹ Some consider that applying too much pressure to the vas with clips or sutures creates ischemia and sloughing of the ligated stump, resulting in recanalization, which could explain some of the higher failure rates seen with these methods.

In an attempt to decrease the risk of postvasectomy chronic pain, some have advocated using a variation of an open-ended vasectomy whereby the testicular end of the vas is left open, the abdominal end is occluded with mucosal cautery, and fascial interposition is then performed. Leaving the testicular end open is proposed to decrease back pressure on the epididymis and decrease the risk of chronic pain, although this has not yet been proved in clinical studies.¹² However, it has been shown to be an effective vasectomy method. Four studies using this technique were found, including one prospective study, with failure rates between 0% and 0.5%.^{20,37,41,42} Leaving out the fascial interposition step with this technique results in a higher failure rate (4%) and is not recommended.⁴³

One other method of vas occlusion has been found to be effective, although it is rarely, if ever, used in the United States. Known as the Marie Stopes International technique, the vas is not divided. Instead, occlusion of the vas occurs after cauterization of the outside of the vas, creating a full-thickness injury on one side and a partial-thickness injury on the other.⁴⁴ The failure rate of this method performed at the Marie Stopes Clinic was reported to be less than 1% after 45,123 vasectomies.

Based on all of this information, no firm conclusion can be drawn as to which occlusion technique is best, but some methods appear to be more effective than others. It is clear that use of fascial interposition reduces rates of vasectomy failure, and mucosal cautery of both ends of the vas seems to consistently result in failure rates of less than 1% whether fascial interposition is used or not. Leaving the testicular end of the vas open has also been consistently effective when the abdominal end is cauterized and fascial interposition is performed. Use of clips or suture ligation with fascial interposition has shown inconsistent results in the literature, and may not be as effective as using mucosal cautery.

The American Urological Association (AUA) released guidelines in 2012 recommending 1 of 4 occlusion techniques should be used, based on available evidence⁴⁵:

- Mucosal cautery of both ends with fascial interposition (without clips or ligatures)
- Mucosal cautery of both ends without fascial interposition (without clips or ligatures)
- Open-ended vasectomy leaving the testicular end of the vas unoccluded, using mucosal cautery on the abdominal end, and performing fascial interposition
- Marie Stopes International technique (nondivisional method of extended electrocautery)

The skin opening can be closed with suture or left open, depending on surgeon preference. Strictly speaking, to be called a no-scalpel vasectomy the skin is not sutured. The authors use one suture to close the wound and apply antibiotic ointment, followed by a sterile gauze and scrotal supporter.

COMPLICATIONS

Complications of infection and hematoma are uncommon using minimally invasive vas isolation, with the rate somewhere on the order of 1% to 2%.^{10,46–48} As discussed earlier, the risk of these complications is less with the minimally invasive techniques than with conventional open vasectomy. There are rare reports of Fournier gangrene occurring postoperatively, one case of which resulted in death.⁴⁹

Debilitating chronic scrotal pain may occur in men immediately or years following their vasectomy, and is sometimes referred to as postvasectomy pain syndrome. In some cases, the pain may be severe enough to adversely affect the quality of life. Patients should be warned of this risk before proceeding with surgery. Various studies differ in the reported rate of postvasectomy pain. The only comparative study showed that 6% of a group of 101 vasectomized men had pain severe enough to seek medical attention, compared with 2% of nonvasectomized men.⁵⁰ Leslie and colleagues⁵¹ found in a prospective audit that among 593 vasectomized men, 0.9% described a pain that affected their quality of life at 7 months postoperatively. Two questionnaire-based retrospective studies with follow-up over 4 years revealed pain affecting quality of life in 2.2% of men in one study, and 5% in the other.^{52,53} Therefore, during the informed consent process each patient should be aware of the small risk of chronic scrotal pain, which appears to be around 1% to 3%.

There has been some discussion about possible association of vasectomy with diseases such as prostate cancer and primary progressive aphasia. Based on available evidence, these claims have not been substantiated. A meta-analysis performed by Dennis and colleagues⁵⁴ showed a possible increased risk for prostate cancer only in the pooled hospital-based case-control studies with a relative risk (RR) of 1.92 (95% confidence interval [CI] 1.37–2.67), whereas pooled cohort studies and population-based case-control studies did not show a statistically significant RR. Another group⁵⁵ performed a systematic review of the literature and reported an RR of 1.23 (95% CI 1.01–1.49), and concluded that no causal relationship was found between vasectomy and prostate cancer. There was significant unexplained heterogeneity among the studies reviewed, and both groups of investigators were of the opinion that there is high risk of selection bias with these studies, which could explain the statistical differences.

Another independent meta-analysis was more recently performed by the authors of the AUA guidelines for vasectomy,⁴⁵ who pooled 10 comparative cohort studies and found an RR of 1.08 (95% CI 0.88–1.32). One group⁵⁶ evaluated the possibility of certain subgroups that may have increased risk, and found that there were no associations between prostate cancer and age at vasectomy, years elapsed since vasectomy, or calendar year of vasectomy. Overall, review of the evidence shows no association between vasectomy and prostate cancer. It is not necessary to discuss prostate cancer routinely with patients considering vasectomy, and men who undergo vasectomy should not be screened differently for prostate cancer.

Primary progressive aphasia (PPA) is a dementia syndrome with aphasia as the presenting symptom, and one small study reported vasectomy to be a possible risk factor for PPA.⁵⁷ The investigators theorized that the link between the two may be related to vasectomy-induced immune response to the tau protein shared by both sperm and brain. A subsequent study did not find an association between antisperm antibodies and cognitive status or language-function status.⁵⁸ Large epidemiologic studies have yet to find an association between vasectomy and dementia, including lack of association with immune-related diseases.⁵⁹ It is therefore unlikely that vasectomy poses a risk for dementia, and patients do not need to be counseled regarding this preoperatively. Numerous studies have also examined a possible relationship between vasectomy and cardiovascular disease, atherosclerosis, stroke, and

testicular cancer.^{60–62} There is no link between these diseases and vasectomy.

POSTOPERATIVE CARE

The authors ask patients to avoid any physical activity for 2 days and to refrain from ejaculation and strenuous activity for 1 week, thus allowing time for luminal occlusion to mature. The procedure does not produce sterility immediately because sperm that could cause pregnancy remain in the reproductive system after vasectomy. Another method of contraception must be used until a favorable PVSA is rendered.

The goal of the PVSA is to rule out vasectomy failure. Vasectomy failure can be due to either technical failure or recanalization. A technical failure can occur by operating on the same vas twice, failing to correctly identify the vas, or, rarely, a duplicated vas deferens. Vasectomy failure is more commonly due to the phenomenon of recanalization. Histologic studies of vasectomy sites after failure reveal 1 or more channels (canaliculi) formed through the scar tissue, which allow passage of sperm. Recanalization can occur early or late. Early recanalization can be picked up on PVSA that shows high numbers of motile sperm. Late recanalization occurs after a man is declared sterile by PVSA, and is usually identified after occurrence of a pregnancy. The risk of pregnancy consequent to late recanalization (known as late vasectomy failure) is approximately 1 in 2000.^{18,45,63–65}

The optimal timing of the PVSA remains controversial. The rationale for early tests is that men can stop using other forms of contraception sooner, whereas later testing will have a greater chance of showing azoospermia and decrease the number of tests. Sperm clearance rates vary across studies, but the majority show azoospermia in more than 80% of men at 12 weeks.^{20,21,66–70} The authors prefer obtaining the PVSA at 12 weeks, but any time from 8 to 16 weeks after vasectomy is appropriate as per the most recent AUA guidelines.⁴⁵ Some have tried irrigation of the vas deferens with saline or water to decrease time to azoospermia, but only 1 of 4 randomized studies showed a benefit with vas irrigation.^{69,71–73}

Some physicians base the timing of the PVSA on the number of ejaculations (eg, 20 ejaculations) since vasectomy. The literature is inconclusive on this matter, and one group's prospective study reported only 44% of patients with azoospermia after 20 ejaculations, with a great degree of variability.³³ Time since vasectomy may therefore be a better parameter for predicting vasectomy success.

Clearance of motile sperm occurs more rapidly than that of nonmotile sperm. When mucosal

cautery is used with fascial interposition, motile sperm are mostly absent by 5 to 6 weeks.^{26,74} Nonmotile sperm can persist in the semen for months after vasectomy because they can reside in the distal vas deferens or seminal vesicles. If a PVSA reveals high numbers of motile sperm, this is due to either early recanalization or technical error. Patients with signs of recanalization may eventually develop azoospermia (vasectomy success) or may have persistently high numbers of sperm, and eventually are deemed a vasectomy failure.

The PVSA can be either given in a laboratory or collected at home and delivered to the physician or laboratory within 1 hour. The sample should then be analyzed within 1 hour of delivery. Only 16% of samples show a decrease in motility between the first and second hour after collection.⁷⁵ Because centrifugation may reduce motility, World Health Organization guidelines (2010) state that centrifugation of the sample should be avoided.⁷⁶ The PVSA can be performed by a laboratory with quantitative analysis, or can be performed by the surgeon in the office setting with high-powered light microscopy. In the case of persistent sperm in the PVSA, determination of sperm concentration is difficult to achieve with office examination.

The presence of nonmotile sperm on PVSA can be troubling for the surgeon. It has been shown, however, that nonmotile sperm in concentrations of less than 100,000/mL on PVSA carry a risk of pregnancy similar to a PVSA with azoospermia.^{40,77} Therefore, patients can discontinue other contraception after one PVSA shows either azoospermia or rare nonmotile sperm ($\leq 100,000/\text{mL}$).

If motile sperm are present on semen analysis, this indicates either recanalization or technical failure. In this case, repeat testing should be performed every 4 to 6 weeks until azoospermia or rare nonmotile sperm is seen, at which time vasectomy can be considered successful. At 6 months postoperatively, motile sperm on PVSA indicate vasectomy failure, and repeat vasectomy should be offered. If greater than 100,000 nonmotile sperm per milliliter are present after 6 months, the decision to repeat the vasectomy is based on clinical judgment and patient preference.

SUMMARY

Vasectomy has proved to be a safe and effective form of sterilization. It is underutilized in comparison with tubal ligation, even though vasectomy is simpler, faster, safer, and less expensive. The preoperative visit prior to vasectomy is important for discussion of expectations and risks, including the less than 1% risk of vasectomy failure and

the need for contraception after the procedure until the PVSA shows successful vas occlusion. The no-scalpel vasectomy technique of vas isolation and its minimally invasive variations have decreased the complication rates for vasectomy. The vas occlusion technique determines the chance of vasectomy success, although there is a lack of high-quality, randomized studies for comparison. Based on the current literature, fascial interposition increases efficacy when combined with another method of vas occlusion, and mucosal cautery seems to be the most effective method of occlusion, resulting in failure rates of less than 1%. Further research comparing these techniques is needed to more clearly identify which methods result in the most desirable vasectomy outcomes.

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Office-Based Sperm Retrieval for Treatment of Infertility

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KEYWORDS

- Office-based • Epididymal sperm aspiration • Testicular sperm extraction
- Testicular sperm aspiration • Microdissection

KEY POINTS

- Sperm retrieval is indicated in men with obstructive azoospermia, nonobstructive azoospermia, and in some cases of severe oligospermia.
- For analgesia and anesthesia, local anesthetic infiltration, spermatic cord regional block, or conscious sedation may be used for office-based procedures. Proper personnel training and facility accreditation are needed to use conscious sedation.
- Appropriate discussion before any procedure, including possibility of repeat procedures, must be held, and if indicated, referral to genetic counseling should be provided.
- Success rates of different procedures for nonobstructive azoospermia depend on histopathology, cause, and procedural approach.
- Complication rates of sperm retrieval procedures are low, but rare clinically apparent side effects may be seen.
- Sperm cryopreservation capability is an important component of sperm retrieval procedures.

INTRODUCTION

Minimally invasive sperm retrieval procedures have become increasingly relevant in the last 2 decades as intracytoplasmic sperm injection (ICSI), a technique allowing conceptions from minimal sperm recovery, has revolutionized success rates of assisted reproductive technology (ART). ICSI was described by Palermo and colleagues¹ in 1992, who reported successful pregnancies in 4 couples with severe male infertility using this technique. The success of ICSI has been shown to be better than conventional in vitro fertilization (IVF) in terms of fertilization rates. Bungum and colleagues² studied fertilization rates in couples with

unexplained infertility who had failed intrauterine insemination. The fertilization rate after ICSI was significantly higher than conventional IVF, at 68% and 46%, respectively. In a randomized study,³ fertilization rate per oocyte after IVF was 41%, whereas the rate after ICSI was 50%. Before development of ICSI, infertility caused by certain male factors, such as nonobstructive azoospermia (NOA), was difficult to treat and had low success rates. However, ICSI has the ability to surpass some of the most challenging cases of impaired spermatogenesis.

Along with development of more efficient ways of sperm implantation came the need to retrieve sperm successfully. Advanced, more refined and

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less invasive sperm retrieval techniques have been developed to provide viable sperm for these difficult cases. Anatomically, the main areas for sperm retrieval are the testis, vas deferens, and epididymis. Choice of target for sperm retrieval depends on the cause of infertility and the likelihood of retrieving viable sperm. For example, the epididymis may be aspirated percutaneously in a man with congenital bilateral absence of vas deferens. Surgical sperm retrieval techniques produce quantities of sperm that are insufficient for intrauterine insemination but may be adequate for multiple trials of ICSI.

For cost-effectiveness and efficiency, office-based procedures are becoming increasingly pertinent. A myriad of surgical techniques to retrieve sperm exist, but not all of them may be used in an office-based setting. Successful office-based procedures require adequate training of surgeons as well as staff. The advantages of performing procedures in an office setting include avoidance of general anesthesia, cost benefit, time efficiency, and quicker patient recovery. The goal of this article is to review office-based sperm retrieval procedures for ART. The indications for sperm retrieval from each anatomic target, preoperative considerations and preparation, surgical details, success rates, factors that play a role in success, and complication rates of each procedure are reviewed.

INDICATIONS FOR SPERM RETRIEVAL

Sperm retrieval is often necessary for azoospermia and severe oligospermia with unfavorable viability. Azoospermia is defined as the absence of spermatozoa in the ejaculate, and severe oligospermia is the presence of fewer than 5 million spermatozoa per milliliter of the ejaculate. Azoospermia is classified into obstructive and nonobstructive. Azoospermia is present in 1% of all men, but 15% of infertile men.⁴ In 1 study,⁵ obstruction caused 40% of azoospermic cases. In obstructive azoospermia (OA), the production of spermatozoa from the testes is normal. However, there is either extrinsic or intrinsic blockage or absence of epididymis, vas deferens, or ejaculatory ducts.

Vasal obstruction may result from previous vasectomy, fibrotic reaction from inguinal hernia repair with mesh, radical prostatectomy, and cystic fibrosis. For men with OA caused by vasal abnormalities, sperm may be retrieved from the vas deferens proximal to the site of obstruction. This procedure is almost always performed in the setting of microsurgical reconstructive surgery, when vasal fluid may be collected and cryopreserved in association with planned vasovasostomy

or vasoepididymostomy. Vasal fluid aspiration may rarely be performed as a separate procedure without reconstruction. Vasal sperm have undergone full maturation as they have traveled through the epididymis.

The epididymis is a more common site used for sperm retrieval. Indications include OA caused by congenital bilateral absence of the vas deferens (CBAVD) or vas deferens occlusion in a setting in which patients are not candidates for or do not desire microsurgical reconstruction. Extraction from the epididymis may be performed percutaneously as well as microsurgically.

Indications for testicular sperm retrieval include NOA, OA with failed reconstructive surgery or epididymal aspiration, and in cases of increased sperm DNA fragmentation and previous unsuccessful IVF/ICSI with ejaculated or epididymal sperm. Testicular sperm extraction may be performed percutaneously, open, or microsurgically.

ANESTHESIA FOR OFFICE-BASED SPERM RETRIEVAL

Office-based procedures require adequate training of all involved personnel, as well as preparedness for emergency situations. Local or regional anesthesia, or conscious sedation, may be used in an office setting. Percutaneous procedures may require only local or regional anesthesia, whereas multifocal, bilateral, or open procedures may need conscious sedation. Patient and physician preference influence final choice of anesthetic.

Local anesthesia involves injecting the skin and subcutaneous tissue with anesthetic medications. It is easy to use, avoids side effects of general anesthesia, and provides adequate local analgesia. Local anesthetics block sodium channels to inhibit the action potential of a neuronal impulse. They can be divided into amide and ester classes. The most commonly used amide is lidocaine, whereas a commonly used ester is tetracaine. If a patient is allergic to lidocaine, an ester class analgesic may be used. Different concentrations of these medications exist, and the lowest concentration needed to provide adequate analgesia should be used. Side effects are a result of intravascular injection and high dose, and include tinnitus, perioral numbness, confusion, seizures, and even cardiovascular collapse.

A spermatic cord block provides regional anesthesia. The block is made by holding the spermatic cord between the thumb and the index finger at the inguinoscrotal junction and injecting 0.5% to 1% lidocaine at 3 different angles around the cord. In addition to a cord block, one must inject the skin at the incision site, because scrotal skin

is supplied by pudendal nerve and a perineal branch of the posterior cutaneous nerve of the thigh,⁶ which are not blocked by the cord block.

Use of conscious sedation in an office setting requires that the facility be accredited by the Joint Commission, Accreditation Association for Ambulatory Health Care, or the American Association for Accreditation of Ambulatory Surgical Facilities.⁷ It also requires appropriate staff training, airway management capability, emergency transfer protocol, and appropriate postprocedural monitoring as well as detailed discharge policies.

PREPROCEDURAL PREPARATION

Before making decisions about the type of procedure for sperm retrieval, it is of the utmost importance to discuss success rates of planned procedure and possible need for additional procedures. In addition, there should be a detailed discussion of possible procedural side effects, including a small risk of clinically apparent hematoma, possibility of changes in testicular volume with a chance of resultant hypogonadism from testicular procedures, infections, hydrocele, and postoperative pain. In addition, the risk of chromosomal abnormalities in offspring from assisted reproductive procedures should be discussed, and if appropriate, genetic counseling should be offered. Any antiplatelet medication should be discontinued 1 week before procedure, unless the risk of discontinuation is exceedingly high. The patient should be advised to abstain from sexual activity for 2 to 3 days to maximize epididymal sperm content. It is advisable to have an accompanying driver on the day of surgery. Close coordination with the andrology laboratory is

required both for immediate cryopreservation, and if the specimen is to be used immediately for IVF.

OFFICE-BASED SPERM RETRIEVAL PROCEDURES

Vasal Sperm Aspiration

For all office-based surgeries described later, it is important to provide adequate anesthesia so that the surgical field is stable without any unintended patient movements. For this reason, extensive microdissection procedures are often performed under general anesthesia. Aspiration of vasal fluid is usually performed at the time of microscopic reconstruction (ie, vasovasotomy, vasoepididymostomy), which requires general anesthesia. On rare occasions, vasal fluid may be aspirated without reconstruction; however, this may complicate future reconstructive surgeries.

After administration of adequate anesthesia, the surgical field is prepared and draped in a sterile fashion. A 1.5-cm skin incision is made along the spermatic cord proximal to the area of vasal obstruction. The dartos fascia is divided with electrocautery and the spermatic cord is identified. The vas deferens is dissected free of surrounding tissues. The vas is partially incised perpendicular to its axis with a Beaver blade down to the lumen and the vasal exudate is collected in the appropriate media by aspiration (Fig. 1). Vasal fluid is examined under the microscope before cryopreservation. The vasal edges may be reapproximated with fine interrupted sutures such as 8-0 or 9-0 nylon. The vas is returned to its correct anatomic position. Dartos fascia and skin are closed with 4-0 chromic suture.

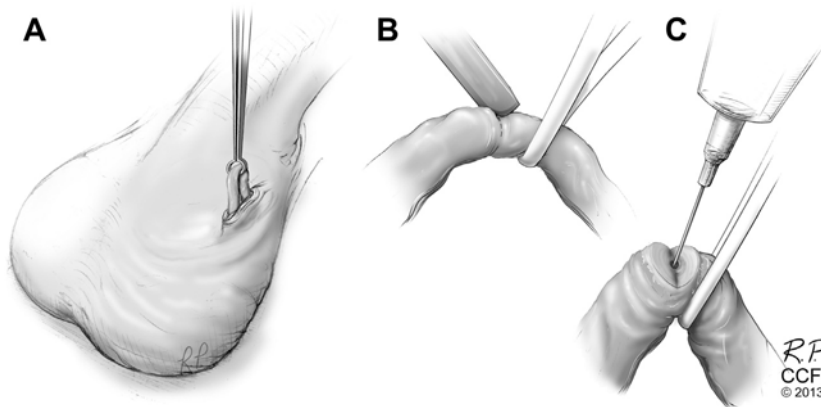


Fig. 1. A 1.5-cm skin incision is made along the spermatic cord proximal to the area of vasal obstruction and vas deferens is isolated (A). The vas is partially incised perpendicular to its axis with a Beaver blade down to the lumen (B) and the vasal exudate aspirated (C).

Percutaneous Epididymal Sperm Aspiration

Spermatic cord block and local infiltration of analgesic medication, or local anesthesia alone, may be sufficient for percutaneous epididymal sperm aspiration (PESA). If needed, an anxiolytic or conscious sedation may be given. PESA is used for men with OA who make a sufficient quantity of sperm and are likely to have an adequate number of sperm in the epididymis. The testis and epididymis are stabilized by 1 hand, and a 23-gauge needle is inserted into the caput or dilated portion of the epididymis with the dominant hand. Negative pressure up to 60 mL is applied, and aspirate is collected (Fig. 2). The aspirate is assessed for presence of sperm, and if needed, the procedure may be repeated on the contralateral side.

Microsurgical Epididymal Sperm Aspiration

Microsurgical epididymal sperm aspiration (MESA) allows direct magnified visualization of the epididymal tubules in an open setting. This procedure

allows selection of the most optimal appearing tubules with the highest expected probability of containing sperm. Regional anesthesia and conscious sedation may be used for this procedure if performed in an office setting. It is also appropriate to perform this procedure under general anesthesia in the operating room. After preparing and draping, a 1.5-cm incision is made in the cranial part of a hemiscrotum. The dartos fascia is divided with electrocautery to assure adequate hemostasis. Testicles and epididymis are reached, and the parietal layer of the tunica vaginalis is divided to bring epididymis into the field. After opening the epididymis, the operating microscope with 20 to 25 optical magnification is brought into the field. A loop of epididymal tubule that appears dilated and opalescent is targeted, isolated, and opened. Epididymal fluid is aspirated, examined, and collected (Fig. 3). The epididymal tubule and tunica are closed with fine suture before closure of the more superficial layers. The surgery may be repeated on the contralateral side if inadequate sperm are found on 1 side.

Testicular Sperm Aspiration

Testicular sperm aspiration (TESA) may be performed with a fine needle (20–23 gauge), large needle (18–20 gauge), or cutting biopsy needle (14–18 gauge). For fine-needle aspiration biopsy (FNAB) and large-needle aspiration biopsy (LNAB), spermatic cord block and local anesthesia or local anesthesia alone are adequate. However, conscious sedation with local anesthesia or cord block is preferred for large-needle cutting biopsy. The

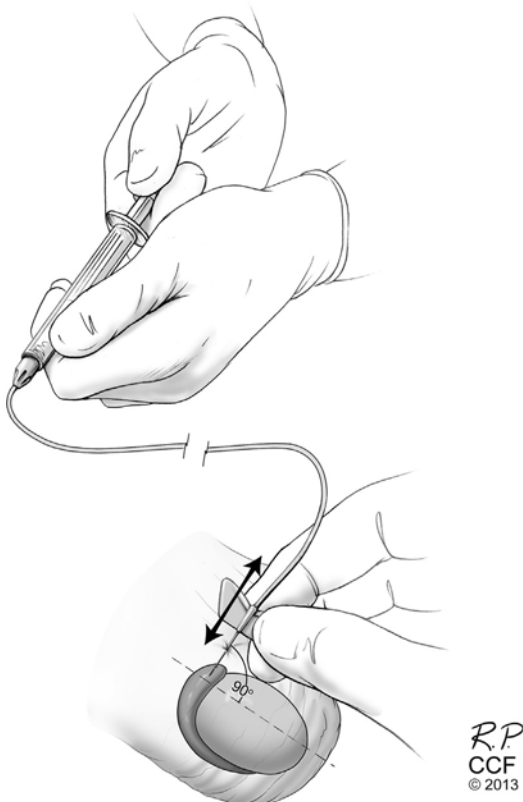


Fig. 2. A 23-gauge needle is inserted into the caput of the epididymis at 90° axis to the testicle. Negative pressure up to 60 mL is applied, and aspirate is collected.

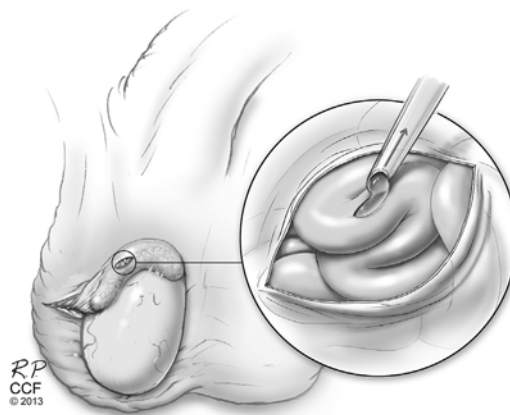


Fig. 3. The epididymis is isolated and the operating microscope with 20 to 25 optical magnification is brought into the field. A loop of epididymal tubule that appears dilated and opalescent is targeted, isolated, and opened, and epididymal fluid is aspirated (*inset*).

testicle is fixed against the scrotal skin and held by the nondominant hand. For FNAB, a 20-gauge to 23-gauge needle is inserted percutaneously into the testicle and negative pressure applied to aspirate and collect sperm. The procedure may be repeated at a different location in the testicle or in the contralateral testicle. For testicular mapping, the upper, mid, and lower poles are sampled several times to assess which area has the best probability of finding viable sperm. The only difference in an LNAB is the use of an 18-gauge to 20-gauge needle. For a cutting biopsy, a biopsy gun with a 14-gauge to 18-gauge needle is used to sample a larger area of the testicle (Fig. 4).

Testicular Sperm Extraction

Conventional open testicular sperm extraction (cTESE) may be performed under regional anesthesia with or without conscious sedation; however, microdissection TESE (mTESE) should be performed under general anesthesia. After preparing and draping the genitalia in a sterile fashion, the testicle is held in place to prevent it from moving. A small incision is made in the anterior midportion of the scrotum. The subcutaneous layers are opened with electrocautery to expose the testicle. A small incision is made in the tunica albuginea in an avascular plane, followed by a gentle squeeze to extrude some seminiferous tubules. The tubules are divided sharply, suspended in a sperm-friendly solution such as synthetic human tubular fluid and

sent for andrology laboratory analysis. The tunica albuginea is closed before closure of the subcutaneous tissue and scrotal skin. This procedure may be performed at multiple sites and repeated bilaterally (Fig. 5). If there is a discrepancy in testicular size, the larger testicle and the one without varicocele is sampled first for greater likelihood of finding sperm.

SUCCESS AFTER SPERM RETRIEVAL PROCEDURES

OA: Vasal Aspiration, PESA, MESA, TESA

For OA, the American Society of Reproductive Medicine (ASRM) and Society for Male Reproduction and Urology (SMRU) believe that sperm retrieval is equally successful from any anatomic target.⁸ All surgeries are acceptable treatment options for patients with OA, including microsurgical reconstruction or sperm retrieval surgeries. The choice between reconstruction and sperm retrieval depends on several factors like female age, need for female reproductive tract reconstruction, or presence of other female infertility factors, as well as likelihood of success with reconstructive procedures. Although the ASRM and SMRU address only PESA and TESA, the success rate of obtaining viable sperm from vasal aspiration ranges from 70% to 100% at first attempt, and 100% at second attempt for OA.^{9,10}

Cause of obstruction does not seem to have an impact on sperm retrieval and live birth rates. A study of 1121 men with OA who underwent sperm aspiration via PESA or TESA showed no difference in successful sperm retrieval rates (SRR) because of cause of obstruction when CBAVD was compared with other causes; in addition, the source of sperm did not have any effect on SRR.¹¹ Similarly, Esteves and colleagues¹² evaluated PESA and TESA in CBAVD, vasectomy, and postinfection patients and found the SRR to be 100%, 96.6%, and 96.3%, respectively. Live birth rates with ICSI were 34.4%, 32.2%, and 34.6%, respectively.

Although the biology of the obstructive process does not influence sperm retrieval, there are certain circumstances when 1 method is preferred over another. The last study showed that PESA was more successful in patients with CBAVD than in vasectomy or postinfectious patients with 96.8%, 69.5%, and 76.4% SRR, respectively. TESA was able to successfully retrieve sperm in the last 2 groups. According to 1 study, PESA is not preferred if there is presence of an epididymal cyst after vasectomy, because the success rate decreases to 20%.¹³ In addition, interval since vasectomy has been shown to affect the outcome of

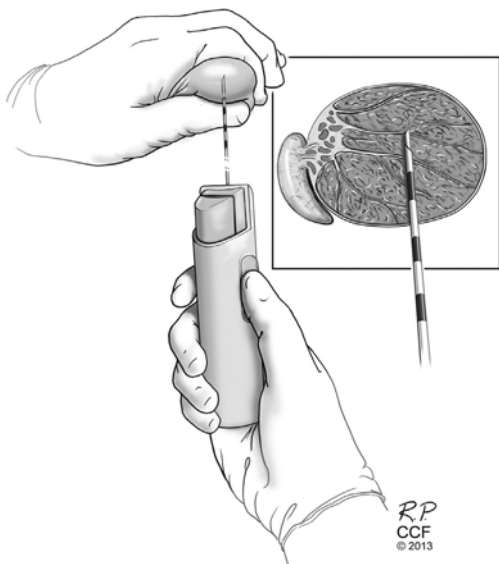


Fig. 4. The testicle is fixed against the scrotal skin and held by the nondominant hand. A biopsy gun with a 14-gauge to 18-gauge needle is inserted percutaneously in a lateral to medial direction (*inset*).

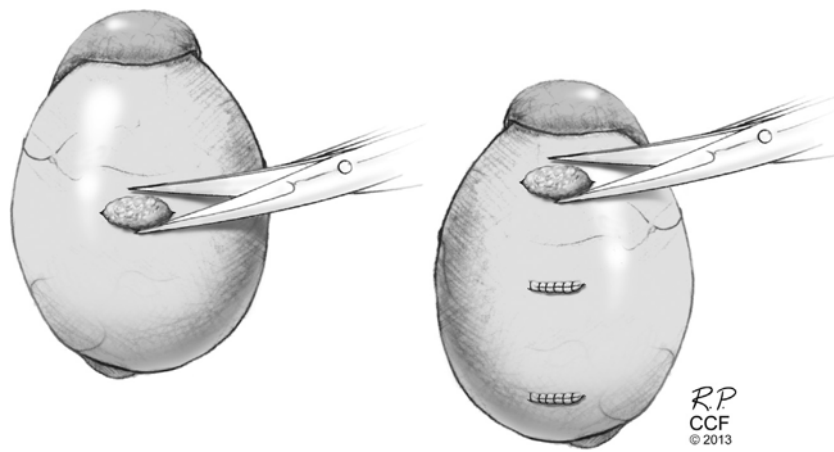


Fig. 5. A small incision is made in the anterior midportion of the tunica albuginea in an avascular plane, followed by a gentle squeeze to extrude some seminiferous tubules (*left*). The tubules are divided sharply. This procedure may be performed at multiple sites (*right*).

microsurgical reconstruction, but it does not seem to alter the success rates in sperm aspiration procedures.^{14–16} Moreover, sperm motility does not seem to affect fertilization and pregnancy rates in patients undergoing ICSI.¹⁷ It is important to note and counsel patients on success of sperm retrieval if no sperm is observed intraoperatively. Per 1 study of mTESE, there is still a 7% chance of finding sperm on tissue digestion in the laboratory.¹⁸

Success rates of PESA range from 61% to 100%.^{12,14,19,20} If a percutaneous approach is not successful, sperm may be retrieved by microsurgical techniques. The success rates for MESA for OA are greater than 90%.^{20,21} The complications of this procedure are minor.

NOA: TESA, TESE

In addition to the particular technique used for testicular sperm retrieval, success is also dependent on histology and cause of NOA. TESA, as described earlier, may be performed with a fine needle, large needle, or cutting biopsy needle. The success rate of FNAB for sperm retrieval ranges from 10% to 64%,^{22–28} a wide range likely attributable to histology, use of multifocal biopsies, and cause of NOA. Cutting needle biopsy has a higher success rate as exemplified by 1 study of 23 men,²⁹ 21 of whom had NOA, in which cutting needle biopsies with 14-gauge and 16-gauge needles revealed the presence of sperm in 56% of the patients.

In cases of failed percutaneous needle testicular biopsies, open biopsies are more successful.²⁷ The success of TESE ranges from 41% to 87%.³⁰ Use of multiple testicular biopsies over

single biopsy is preferred because of higher success rate. Twenty-nine men underwent testicular biopsies in 55 testes at 3 predetermined areas (ie, rete testis, midline, and proximal regions). Overall success rate was 50.9% (28/55 testes). Sperm were retrieved from 3, 2, or 1 region in 53.6%, 17.9%, and 28.6% of the testes.³¹ If only 1 area had been biopsied, SRR would have been approximately halved. Another study compared single biopsy from both testicles with 2 to 4 biopsies from each testicle in 316 and 100 patients, respectively. The SRR was 37.5% with single bilateral biopsies compared with 49% with multiple bilateral biopsies.³²

When comparing cTESE with mTESE, the latter technique tends to have superior results. In a study by Amer and colleagues,³³ 100 men with NOA with matched histopathology underwent cTESE on 1 testicle, and mTESE on the opposing side, and showed SRR of 30% and 47%, respectively. These results showed that with the same histopathologic background, mTESE has superior performance to cTESE. In a series of 98 patients with NOA,³⁴ 24 patients had sperm retrieval by cTESE, whereas 74 patients underwent mTESE. The SRR was 16.7% and 44.6%, respectively. In a randomized trial, cTESE was compared with mTESE in 194 testicles. Variables compared included follicle-stimulating hormone (FSH), histopathology, and testicular volume. Each testicle was classified according to these variables into a 48-square table. Data between cTESE and mTESE groups were randomized and matched. The investigators found that a surgical approach had a significant effect on finding sperm; however, most of the difference was seen in the Sertoli cell only group (27.5% and 12.5% for mTESE vs cTESE, respectively),

whereas other groups had similar rates with both techniques.³⁵

Role of Histopathology

Histopathology plays a major role in predicting the success of sperm retrieval in patients with NOA. Hypospermatogenesis has the most success (70%–100%), followed by maturation arrest (MA) (44%–75%), with the least success seen in Sertoli cell only (also known as germinal cell aplasia) syndrome (16%–50%).³⁰ Some investigators make a distinction between early and late MA. Early MA is defined as arrest in the spermatogonia or spermatocyte phase, whereas late MA is during the spermatid phase.^{36,37} In a study of 223 men with NOA,³⁶ 34 were identified as having MA, of whom 21 had early MA and 13 had late MA. These investigators found that patients with early MA had greater frequency of genetic anomalies, compared with patients with late MA, who had a higher likelihood of a previous testicular insult (varicocele, cryptorchidism, heat exposure, and testicular trauma). Patients underwent cTESE as well as mTESE, although the technique did not seem to influence the SRR in this study. The sperm retrieval in early MA versus late MA was successful in 23.5% and 53.8% of patients, but this difference was not significant, likely because of small number of cases. In another study,³⁷ 49 of 219 men with NOA were found to have MA. Men with late MA had increased testosterone, lower FSH level, and higher SRR than early MA, 65.5% versus 30%, respectively.

Use of mTESE results in higher success rate in some of these histopathologic diagnoses. Okada and colleagues³⁴ showed that men with MA treated with cTESE versus mTESE had successful sperm retrieval in 37.5% and 75%, respectively. Superior results were also seen in men with Sertoli cell only syndrome with mTESE compared with cTESE, with the SRR being 33.9% and 6.3%, respectively. Comparison of hypospermatogenesis was not available because no men with that histopathology underwent cTESE, although these men had 100% success with mTESE.

Sperm Retrieval in Patients Who Have Cancer

Retention of fertility is an important issue for cancer survivors. Fewer than half of the physicians treating patients who have cancer refer them for fertility preservation before initiation of therapy.³⁸ The type and duration of therapy, and pretreatment reproductive function, influence posttherapy fertility potential. In a study by Hsiao and colleagues,³⁹ 73 men with variable cancer types who received different chemotherapies underwent

84 mTESE procedures. Mean age of the men was 34.5 years, mean FSH level was 21.9 U/L, average testicular volume was 9.1, and average time from chemotherapy to TESE was 19 years. Of the patients who received a diagnostic testicular biopsy, 90% had Sertoli cell disease, whereas the remaining 10% had hypospermatogenesis. The SRR was 43% (36/84 surgeries), with the highest in patients who had testicular cancer and lowest in patients with sarcoma. Other smaller studies have shown similar results, with SRR of 42%⁴⁰ and 65%,⁴¹ although in the latter study, frequency of Sertoli cell only histologic type was lower, at 48%.

Klinefelter Syndrome

Another cause that may play a role in sperm retrieval success is the diagnosis of Klinefelter syndrome. The chromosomal abnormality may be caused by meiotic nondisjunction, 47, XXY or mosaicism, 46, XX/47, XXY. Men with mosaicism have a greater chance of having rare sperm in their ejaculate than nonmosaics. These men have small firm testes, and small focal areas of spermatogenesis. TESE has made it possible to retrieve sperm from this cohort, with superior results seen with mTESE. In a study by Vernaev and colleagues,⁴² 50 nonmosaic men underwent cTESE, and SRR was 48%. None of the factors including FSH, testosterone, facial hair pattern, gynecomastia, or testicular volume were predictive of success. In another study, 24 nonmosaic patients with Klinefelter syndrome underwent cTESE with 33% SRR. FSH, inhibin B, and testosterone levels did not have any predictive value; however, age younger than 32 years was predictive of greater success.⁴³ A larger study using mTESE to extract sperm in 68 men with nonmosaic Klinefelter syndrome found an SRR of 66%.⁴⁴

Y Microdeletions

Another type of chromosomal abnormality that is found in about 10% of men with severe oligospermia or azoospermia is Y chromosome microdeletion. Complete and partial deletions of 3 regions, AZFa, AZFb, and AZFc, have been described. Sperm retrieval has not been successful in patients with complete AZFa or AZFb deletions. Patients with AZFc mutation have better results; mTESE in AZFc patients showed an SRR of 71% in 1 series.⁴⁵

Role of Hormonal Treatment in NOA

To increase the success rate of sperm retrieval in men with NOA, hormonal treatment before the procedure has been attempted. A study by Shiraishi and colleagues⁴⁶ evaluated 48 men

who had 1 failed mTESE. Twenty-eight men were treated with human chorionic gonadotropin (hCG), whereas 20 men did not undergo any hormonal treatment. There was a significantly greater SRR at second mTESE among men who had hormonal treatment (21%) when compared with those who did not (0%). On the contrary, a larger study of 736 men with NOA consisting of a cohort of men who had testosterone level less than 300 ng/dL and were treated with clomiphene citrate, hCG, or aromatase inhibitors, found no significant difference between those who responded to treatment versus those who did not.⁴⁷

Predictive Models for Sperm Retrieval

Some have attempted to build predictive models to assist in making decisions about pursuing surgical sperm retrieval based on predicted success rate. In a study by Tsujimura and colleagues,⁴⁸ 9 preoperative factors were analyzed in a cohort of 100 men with NOA who underwent mTESE. Nine parameters were tested, including age, testicular volume, FSH, luteinizing hormone (LH), inhibin B, total testosterone, free testosterone, and estradiol. These investigators found that FSH, total testosterone, and inhibin B were significantly associated with successful sperm retrieval by mTESE. They developed a formula using these variables that could be used to predict presurgery probability of success. The formula is as follows: $P = 5 [1 + \exp(5.201 - 0.048 \times \text{FSH} - 0.449 \times \text{total testosterone} - 0.021 \times \text{inhibin B})]^{-1}$. The correlation between predicted probability and observed success was 0.77. This equation had a sensitivity of 71% and specificity of 71.4%. This study used noninvasive parameters, which makes this equation easy to use. However, it remains to be validated in another cohort before it is used widely.

Another study⁴⁹ developed an artificial neural network model incorporating age, FSH, LH, testosterone, prolactin, left and right testicular volume, and duration of infertility for predicting sperm retrieval success after bilateral multiple biopsy conventional TESE. The diagnostic accuracy of this model was 80.8%. In a recent study,⁵⁰ a nomogram was developed using a cohort of 1026 men with NOA. The parameters included in their nomogram were patient age, FSH, history of cryptorchidism, Klinefelter disease, left testis volume, and presence or absence of a varicocele. History of cryptorchidism and Klinefelter disease had the biggest role in predicting positivity based on this nomogram. However, on internal validation, the accuracy of the nomogram was only 59.6%. The investigators concluded that the model could not be used to reliably predict presence of sperm on

mTESE. These models are intriguing but require further investigation.

Varicocele and NOA

An issue in NOA is the presence of a varicocele. It is controversial whether a varicocelectomy should be performed in men with NOA. Studies investigating this issue have been retrospective in nature, with mixed results. One study⁵¹ compared a group of men with NOA who underwent varicocelectomy with a group who did not and found that SRR on mTESE was significantly higher in the former group, at 53% versus 30%, respectively. In another study of 96 men,⁵² similar results were seen, and sperm retrieval was higher in the group who underwent varicocelectomy (61%) compared with those who did not undergo surgery (38%). However, another study⁵³ showed equal sperm retrieval success in those who did or did not undergo a varicocelectomy. A meta-analysis⁵⁴ of 11 studies including 233 patients who had varicocele repair using a variety of techniques showed that 39% of men had return of motile sperm in their ejaculate, and the resulting pregnancy rate was 10%. The issue of varicocele repair in the setting of NOA remains a matter of debate and requires further research.

COMPLICATIONS

Overall, the complications from surgical sperm retrieval procedures are rare and generally minor. The complication rates for PESA range from 0% to 9%.^{55,56} Postoperative pain is the most common complication, whereas hydrocele, hematocoele, and epididymitis are less common. Similarly, the complications with MESA are unusual and low in severity.

FNAB of the testis is a safe procedure, with rare possibility of bleeding. In a study by Carpi and colleagues,⁵⁷ 387 testicles were sampled with FNAB or LNAB, and there were no clinical complications, no requirement of narcotic pain medications, and no day off work after the procedures. A cutting biopsy with an 18-gauge needle was performed in 31 patients, and only 3 required narcotic pain medication. None developed a hematoma or needed time off work. In a study in which 14-gauge and 16-gauge needles were used,²⁹ there were no complications except minor pain and swelling.

TESE has been shown to cause structural changes when follow-up testicular ultrasonography is performed. Subclinical hematomas, fibrosis, devascularization, and change in testicular size have been seen after the procedure. Clinically relevant changes are infrequent and may include testicular atrophy and hypogonadism, with need

for testosterone replacement therapy. Overall, the complication rate has been shown to be lower in mTESE than cTESE. cTESE results in more changes detected by ultrasonography, as seen in 1 study,³⁴ which showed that 51% of men treated with the conventional technique had a hematoma on ultrasonography at 1 month compared with 12% with microdissection technique. Clinically, significantly more men with lower testicular volume were seen in the cTESE group than the mTESE group (25% vs 2.5%, respectively). One patient (2.5%) in the former group had bilateral testicular atrophy and subsequently needed testosterone replacement therapy. In contrast, another study⁵⁸ did not find a significant difference in the rate of hypogonadism between cTESE and mTESE techniques at 18-month follow-up after the procedures.

SUMMARY

Office-based sperm retrieval procedures are becoming increasingly relevant, because they provide patient and surgeon convenience and are cost-effective. The development of ICSI has introduced an increasing need for sperm recovery in even the most challenging cases of male infertility. Men with azoospermia represent a significant part of the infertile population. Men with OA may undergo vasal or epididymal sperm retrieval, whereas men with NOA require removal of sperm from the testicle. Sperm retrieval may be performed open or microsurgically; the success rate is higher with microsurgery. Other factors that influence success of sperm retrieval in NOA include the histopathology and cause of NOA. Complications are minor; the rate of complications is low with most procedures. Before undertaking any office-based procedures, all office personnel must be fully trained and the facility must be appropriately accredited.

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Electrical and Mechanical Office-based Neuromodulation

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KEYWORDS

• Overactive bladder • Neuromodulation • Sacral nerve • Tibial nerve • Electric stimulation therapy

KEY POINTS

- Neuromodulation techniques, such as sacral neuromodulation (SNM) and percutaneous tibial nerve stimulation (PTNS), are treatment options for patients who fail behavioral therapy and pharmacotherapy.
- Neuromodulation may augment inhibitory bladder afferents and lead to cortical plasticity to inhibit bladder reflexes.
- A test sacral stimulation can be performed in the office with temporary leads and may help identify patients who are most likely to succeed with SNM.
- PTNS is an emerging therapy that may improve OAB symptoms in some patients through entirely office-based neuromodulation.

INTRODUCTION

Chronic urinary frequency, urgency, and urge incontinence represent common problems in the urologist's practice. The term overactive bladder (OAB) is defined by the International Continence Society as "urgency or frequency with or without urge incontinence in the absence of other pathologic or metabolic conditions to explain these symptoms."¹ An estimated 34 million people in the United States have OAB,² leading to significant impairment in quality of life, a higher risk of falls and other accidents, and lower self-esteem and health perception.³ Annual cost associated with OAB is estimated at more than \$9 billion, including direct care, health consequences, and lost productivity.⁴

For patients with OAB, first-line treatment options include conservative therapies, such as pelvic floor exercises and biofeedback, along with pharmacologic therapy. Although many patients find relief with these therapies, up to 40% of patients are either refractory to primary management or have an unsatisfactory response.⁵ Currently, several options exist for these patients, ranging from intradetrusor injection of botulinum toxin to

irreversible surgical therapy, including detrusor myomectomy, augmentation cystoplasty, and urinary diversion. Neuromodulation represents a minimally invasive and reversible treatment with a high rate of success for patients who are refractory to first-line therapies for OAB.

In this review, we focus on office-based neuromodulation, specifically percutaneous tibial nerve stimulation (PTNS) and office-based test procedures for sacral neuromodulation (SNM). SNM refers to electrical stimulation of the S3 (or S4) sacral nerve root to modulate the micturition reflex. Initially, a test procedure is performed using either temporary leads placed in the office or, alternatively, permanent leads placed in the operating room (OR). After a successful test period, permanent leads and a pulse generator are implanted in the OR. PTNS is a less invasive, office-based therapy that applies electrical stimulation in a retrograde fashion through the tibial nerve to achieve neuromodulation of the sacral plexus. PTNS is typically applied weekly in the office for 12 weeks and responders continue with monthly therapies.

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Historical Perspective

Neuromodulation therapy for OAB is a recent step in the long history of the use of electrical stimulation for medical purposes. In the nineteenth century, electrical stimulation was used for a broad range of psychiatric disorders and later applied to the bladder, pelvic floor, or sacral roots for neurogenic urinary retention or overactivity. Advances in cardiac pacing led to miniaturization of electrical instruments and the first demonstration of sacral neuromodulation by Drs Tanagho and Schmidt⁶ in the early 1980s. In patients with neuropathic voiding dysfunction, they showed that continuous stimulation of sacral root S3 modulated detrusor and sphincter activity, resulting in stabilization of micturition reflexes.

Further pioneering work on the mechanism of action of SNM was performed by Drs Craggs and Fowler in London⁷ and Drs DeGroat and Chancellor at the University of Pittsburgh.^{8,9} Initial large-scale trials (Medtronic [MDT]-130) demonstrating the efficacy of SNM in patients with non-neuropathic OAB were funded by Medtronic (Minneapolis, MN) in the mid-1990s. On the basis of these trials, the US Food and Drug Administration (FDA) approved SNM for urge incontinence in 1997, then urgency/frequency and nonobstructive urinary retention in 1999. Since then, SNM has been successfully used in about 25,000 patients with OAB.¹⁰

More recently, PTNS has emerged as a lower-cost, office-based form of neuromodulation after pioneering work in the late 1980s by Dr Stoller at the University of California, San Francisco.¹¹ Recently, a few randomized controlled trials have demonstrated improvements in urinary symptoms above those of placebo¹² and similar to improvements with tolterodine.¹³ Subsequent studies have demonstrated a durable response in some patients.¹⁴ Currently, a commercial neuromodulation system is produced by Uroplasty, Inc (Minnetonka, MN), which received 501(k) FDA marketing clearance for urgency/frequency and urge incontinence in 2005.

Mechanism of Action

The exact mechanism of action of neuromodulation on micturition remains unclear. In theory, neuromodulation acts to augment inhibitory somatic afferents that are deficient in patients with OAB.¹⁵ These bladder afferents project to the pontine micturition center and, with chronic stimulation, lead to changes in suprapontine regions that ultimately modulate micturition reflexes.¹⁶ In SNM, electrical stimulation is directly applied to the sacral nerve root.

Chronic sacral nerve stimulation has been shown to lead to augmented somatosensory cortical responses to evoked potentials along the pudendal and posterior tibial nerves.¹⁷ PTNS aims to achieve an effect similar to SNM on micturition reflexes through electrostimulation of the posterior tibial nerves. Chronic electrostimulation of the pudendal nerve has also been shown to improve OAB symptoms in a few patients with neurogenic OAB.¹⁸

Through positron emission tomography studies, additional neural plasticity is observed over the course of neuromodulation in cortical areas associated with motor learning and with pelvic floor and abdominal musculature.¹⁹ Thus, an additional theory is that neuromodulation also acts by augmenting of the guarding reflex. In animal models, neuromodulation leads to hypertrophy of striated external sphincter muscle fibers and to increased urethral closure pressures. It is unclear if these changes are due to the proposed neuromodulatory effect or simply due to direct stimulation of motor pathways by Onuf nucleus.²⁰

INDICATIONS

Neuromodulation is indicated for the treatment of refractory urge incontinence and urinary frequency/urgency syndromes. Generally, patients who have failed or who could not tolerate pharmacotherapy and conservative therapy are candidates for a trial of neuromodulation. Conservative therapy may include behavioral modification, pelvic floor rehabilitation (including pelvic floor biofeedback/muscular vaginal electrical stimulation). Some physicians exhaust all possible options, including high-dose combinations of antimuscarinics and tricyclic antidepressants, before considering neuromodulation; others will move to neuromodulation earlier. Bladder botox therapy has also been approved for these patients who have failed behavioral and pharmacotherapy.

The recently published American Urologic Association Guidelines include both SNM and PTNS as third-line, FDA-approved treatments for patients with non-neurogenic OAB. The Grade C recommendation applies to carefully selected patients who have severe refractory OAB symptoms or those who are not candidates for pharmacotherapy.²¹ In 2009, the International Consortium on Incontinence published an algorithm for the management of patients with OAB. SNM is the only minimally invasive treatment option for refractory OAB with a Grade A recommendation (high level of evidence). These recommendations are based on randomized controlled trials (reviewed later in this article) of SNM for urgency/frequency

and urge incontinence demonstrating safety and efficacy along with subsequent follow-up studies demonstrating a durable response. Several randomized trials have shown short-term improvement in OAB symptoms with PTNS,^{12–14} although there are fewer data on long-term efficacy. European Association of Urology (EAU) guidelines gave a grade B recommendation to offer PTNS for improvement of urge incontinence in women who have not benefited from antimuscarinic medications.²²

Painful Bladder Syndrome and Neurogenic Voiding Dysfunction

In the United States, the current approval for SNM is for the treatment of refractory urinary frequency/urgency syndromes, urinary urge incontinence, and nonobstructive urinary retention of a non-neurogenic etiology. However, since the introduction of SNM for OAB, there has been growing recognition of the potential benefit of SNM for a broader range of pelvic disorders that may involve some OAB symptoms. Research is ongoing into the potential use of SNM for interstitial cystitis/painful bladder syndrome (IC/PBS) and neurogenic voiding dysfunction among others.

Patients with IC/PBS may experience an improvement in coexisting urinary symptoms with SNM. One series demonstrated short-term improvement in urinary symptoms along 27 carefully selected patients who had successful test stimulation.²³ In another study of carefully selected patients with IC/PBS managed with SNM, 50% of patients underwent explantation for pain at the implantation site, infection, or other reasons. Of the patients who did not undergo implantation, there was minimal loss of benefit over 59.9 months of follow-up.²⁴ SNM may be suitable for some patients with primarily urinary symptoms and minimal pain.

Patients with neurologic disease were excluded from the initial industry-sponsored trials and subsequent follow-up studies based on the belief that an intact spinal pathway was necessary for neuromodulation. However, similar success rates are observed in patients with neurogenic OAB²⁵ and there is some evidence to support early intervention with SNM after spinal cord injury to prevent urinary incontinence.²⁶ One major practical limitation of SNM for neurologic disorders is the need of many of these patients to undergo magnetic resonance imaging studies.

Psychiatric Considerations

Comorbid psychological disorders are common among patients who are candidates for SNM

therapy. Although many patients will have substantial physical and psychological benefit from successful therapy, a history of psychiatric disorders may influence the rate and duration of a successful response to SNM therapy. In an early study of 36 patients undergoing SNM, patients with a history of mental illness were more likely to fail implantation after a successful test procedure (82% vs 28%). Furthermore, patients with a history of mental illness had a shorter duration of therapeutic effect from SNM compared with patients with no history (12 vs 36 months).²⁷

Conversely, voiding symptoms impose a clear burden on quality of life and may contribute to the presence or severity of psychological or mental disorders. Improvement in OAB symptoms through neuromodulation may improve or prevent deterioration of mental health. The MDT-103 trial demonstrated a clear benefit in terms of depression and health-related quality of life after SNM therapy. Of the 89 patients in the trial, 73% had some degree of depression at baseline. Patients assigned to direct implantation showed significant improvement in the Beck Depression Index after SNM therapy at 3, 6, and 12 months after starting therapy, whereas patients in the delayed group showed a slight worsening of depression symptoms.²⁸

These data suggest that significant psychological benefit may be gained from successful SNM therapy. However, in some cases, such as when there is concern that preexisting psychological disorders may interfere with response to therapy, a psychiatric evaluation may be warranted.

SACRAL NEUROMODULATION TEST PROCEDURE

A test procedure provides a short-term trial of SNM and is important to patient selection before permanent implantation of an implantable pulse generator (IPG). The response during the test period can be used to select the optimal lead position (left vs right, S3 vs S4) and establish patient expectations for symptomatic improvement. The test procedure can be performed with temporary leads in the office under local anesthesia. Although the pioneers of SNM performed this test procedure without fluoroscopy, most practitioners perform it under fluoroscopic guidance. Alternatively, a test procedure using permanent tined leads can be performed in the ambulatory-surgery unit or operating room.

In either case, the patient performs a 2- to 3-day voiding diary before the test procedure. The test period lasts for a few days up to 1 week for temporary and 2 weeks for permanent tined leads. The wires are attached to an external stimulator. The

patient maintains stimulation at a comfortable level (it should not be painful) and completes a voiding diary to provide objective data. Based on the patient's experience and voiding diary, a final decision is made to proceed or not to proceed with permanent implantation. Usually, the patient needs to exhibit significant subjective improvement, and the voiding diary should show at least 50% improvement in voiding parameters to warrant proceeding to implantation of the IPG.

Office-based Procedure

The office-based test procedure sometimes is referred to as percutaneous nerve evaluation. The patient is placed in the prone position with 1 or 2 pillows under the lower abdomen to improve the sacral approach. The sacrum is prepped with antiseptic solution and the sacral notches and coccygeal drop-off are identified by palpation or fluoroscopy. S3 usually is located 1.5 to 2.0 cm lateral to the midline at the level of the sacral notches, or about 9 cm above the coccygeal drop-off. Local anesthesia is achieved from S2 to S4 over the underlying skin and subcutaneous tissue, making certain not to enter the foramen.

Insulated foramen needles are placed percutaneously in the S3 and S4 foramen using the previously mentioned landmarks and fluoroscopic guidance (with primarily lateral imaging). Appropriate sensory and motor responses are identified. Once the appropriate responses have been obtained, an insulated wire is placed through the 18-gauge needle in the foramen and the needle is removed. These temporary wires are inexpensive and easy to place. For patients without a clear optimal site of lead placement, 2 or more such wires can be taped in place and attached to an external stimulator. The patient is taught how to adjust for optimal results and can try out left and right sides of S3 and S4 and decide on the best response. Bilateral test stimulation may be helpful for some patients who fail an initial trial with unilateral placement.²⁹

Sensory and Motor Neural Responses

Intraoperative motor and sensory neural responses guide lead positioning during the test stimulation. Sensory responses generally include a tingling, pulling, or vibratory sensation in the vagina and rectum in women and in the scrotum, phallus, and rectum in men. Motor responses include levator tightening (bellows response) and plantar flexion of the big toe. Sometimes at S3, a plantar flexion of the entire foot is noted. In such cases, S4 may be the more appropriate foramen,

as most patients are significantly bothered by such a foot response.

An intraoperative motor response during the test procedure generally is considered to be more predictive of success after IPG implantation than a sensory response. Cohen and colleagues³⁰ followed 35 patients, 21 of whom progressed to permanent IPG implantation after a test procedure using quadripolar tined leads. A positive motor response was observed in 95% of those progressing to permanent implantation versus only 21.4% of patients who failed the test procedure. Patients with a positive sensory response in the absence of a motor response had only a 4.7% chance of having a positive result after implantation. Another recent study examined the role of sensory testing in patients with both OAB and pain symptoms, a group that might be expected to benefit from sensory testing. There was no difference in the rate of symptomatic improvement or explantation for patients who did or did not have sensory testing.³¹

Although intraoperative motor responses are the primary neural responses used to locate the ideal site of electrode implantation, neuromodulation is usually applied at a level below that needed to stimulate a motor response. The patient may use sensory perception to stimulation as an indicator of continued neuromodulation. Loss of sensory perception after implantation may herald a loss in benefit from neurostimulation.

Office-based Test Procedure Versus 2-Stage Implant

A major consideration for the clinician is whether to pursue an office-based test procedure, which if successful, is followed by a "1-stage" implant of permanent leads and an IPG in the OR. An alternative approach is the "2-stage" procedure, in which the patient has permanent quadripolar tined leads implanted in the OR. The patient undergoes a trial period, and if successful then returns to the OR for tunneling of the leads and placement of an IPG.

Before the development of a test procedure with permanent quadripolar leads, use of a temporary lead was the only means for patient selection for SNM. The test procedure itself is considered safe, and complications at the preimplantation stage are rare; however, lead migration and the risk of infection limit the trial period to about 1 week.³² Lead migration often presents with pain and decreased efficacy and occurs at a rate of about 10% to 15%. Other complications, including pain, may occur at a lower rate (about 2%–3%).³³ It is not clear if these failures are due to undetected lead migration, infection, or other reasons.

Since the introduction of permanent quadripolar tined leads for test stimulation in 1997, multiple groups have published on the successful use of these leads. The major advantage of the 2-stage procedure is that the final lead-nerve interface is established before the test period. In theory, the tines should prevent lead migration and thereby allow a longer test period of up to 2 weeks. A recent meta-analysis of SNM trials found a 16% rate of lead migration.³⁴ Overall, it appears that the use of tined leads may decrease, but not eliminate the risk of lead migration during the test period, particularly for thin patients.³⁵ The primary disadvantage of a 2-stage procedure is that this procedure requires 2 trips to the OR and may be associated with a higher cost.

A few studies have directly compared outcomes using temporary leads in the office compared with permanent tined lead placement in the OR. In one recent nonrandomized study, patients undergoing a 3-day test period with temporary leads were less likely to progress to implantation than patients who underwent a test procedure with tined leads. However, among those patients who progressed to implantation, the type of test procedure did not impact failure rates, which were below 3% for both groups over 24 months of follow-up.³⁶ Similar results were found in a smaller, randomized study involving only women.³⁷

A longer trial, up to 2 weeks, appears to increase eligibility for implantation, possibly because it takes some patients a longer time to adjust settings or otherwise achieve therapeutic benefit.³⁸ Although a trial period of 1 to 2 weeks with tined leads does not seem to increase the specificity of a successful trial compared with an office-based trial, there may be a benefit from very long trial periods. Everaert and colleagues³⁹ randomized 41 patients to either an office-based test procedure or to a 3-week to 5-week trial period after placement of tined leads in the OR. At 24 months of follow-up after implantation, there was a lower

rate of failure for patients undergoing the prolonged test procedure compared with those who had only an office-based test procedure (14% vs 33%). In that study, the costs of an office-based test procedure were about \$2,667 less than a test procedure initiated in the OR. Our own data (Table 1) suggest that in experienced hands, an office-based fluoroscopically assisted test procedure provides excellent results, and can be performed in most patients at a much reduced cost to the health care system and is also an overall more efficient use of surgeon and OR time.

In practice, trial periods longer than 2 weeks are uncommon, primarily because of the potential for increased risk for infection. Huwlyer and colleagues⁴⁰ performed a microbiologic examination of explanted tined leads from 20 patients who underwent an unsuccessful test period for 2 weeks or longer and identified *Staphylococcus* species growth in 4 patients. However, these bacteria were susceptible to perioperative antibiotics and only 1 of these patients had clinical signs of infection. Furthermore, the manufacturer recommendation is not to exceed a 2-week trial period.

Overall, it seems that an office-based test procedure remains a reasonable option for most patients, and that a successful test procedure generally portends a good outcome after implantation. A test procedure with tined leads placed in the OR may be more suitable for patients in whom the test procedure is equivocal, patients who may require a longer test period to evaluate efficacy, and for patients in whom lead migration is suspected.

PERCUTANEOUS TIBIAL NERVE STIMULATION

The posterior tibial nerve is a mixed sensory-motor nerve, with axons from L4 to S3 spinal roots. The sacral roots contain peripheral nerves involved in motor and sensory control of the bladder, the same nerves involved in SNM. Electrical

Table 1
Outcomes and rate of progression to IPG implantation after office-based SNM test stimulation for 52 patients at our institution

	Frequency, Urgency (n = 24)	Urge Incontinence (n = 24)	Nonobstructive Retention (n = 4)
>50% Sx improved, n (%)	14 (58)	17 (71)	1 (25)
Permanent IPG, n (%)	13 (54)	13 (54)	1 (25)
Equivocal, n (%)	3 (13)	0 (0)	1 (25)
Permanent IPG, n (%)	2 (8)	0 (0)	0 (0)
Did not respond, n (%)	7 (29)	7 (29)	2 (50)

Abbreviations: IPG, implantable pulse generator; SNM, sacral neuromodulation; Sx, symptoms.

stimulation of these nerves inhibits bladder activity, which then evokes a central inhibition of the micturition reflex pathway in the spinal cord and brain.

McPherson first demonstrated in a cat model in 1966 that stimulation of cut ends of peripheral nerves including the posterior tibial nerve inhibited bladder contractions.^{40–42} Then in 1983, McGuire and Morrissey applied electrical stimulation of hind-quarter nerves to treat detrusor instability in spinal cord injured nonhuman primates.^{43–45} They went on to demonstrate efficacy in humans.⁴⁶

PTNS treatments generally use a 34-gauge needle electrode that is inserted approximately 5 cm cephalad to the medial malleolus and slightly posterior to the tibia. The needle is inserted at a 60° angle. A surface electrode is placed on the calcaneus of the same (ipsilateral) foot. The electrode and needle are connected to the stimulator, which is set at a current of 0.5 to 9.0 mA at 20 Hz, based on motor and sensory responses. The patient generally undergoes treatment for 30 minutes weekly for 12 weeks. This is followed by treatments as needed based on patient symptoms.

EFFICACY AND OUTCOMES

SNM

A recent review of the initial randomized controlled trials of SNM for urgency/frequency and urge incontinence found an overall initial response rate of between 64% and 88%.¹³ In a separate review and meta-analysis, 80% of patients had either 90% continence or a 50% improvement in urge incontinence in response to SNM.³⁴ The response to SNM appears to be durable. In a prospective international trial of 121 patients who had an initial response after 1 year of therapy, 84% of patients with urge incontinence and 71% of patients with urgency/frequency showed a persistent response at 5 years (>50% reduction in symptoms).⁴³

Three prospective randomized trials of SNM for urgency/frequency or urge incontinence merit mention. A study by Schmidt and colleagues⁴⁶ enrolled 155 patients from 16 international centers with urge incontinence refractory to medications and without pelvic pain or known neurologic conditions. All patients underwent a test period of 3 to 7 days and 98 patients had a greater than 50% improvement in their symptoms. These patients were randomized to undergo either immediate IPG implantation or delayed implantation after 6 months of medical therapy. After 6 months of SNM for the immediate implantation group, 47% of patients were completely dry and 29% had a greater than 50% reduction in incontinence with efficacy retained at 18 months of follow-up.

Urodynamic parameters improved for the immediate versus delayed implantation group at 6 months with a higher percentage demonstrating stable detrusor function (56% vs 16%; $P = .014$). For all patients, 32.5% underwent surgical revision for generator or implant site pain or lead migration.

A second trial on SNM for urge incontinence randomized 44 patients to SNM or medical management with an average reduction of 88% in episodes of incontinence and 90% in leakage severity; 56% of implant patients versus 4% of controls had complete resolution of incontinence, and urodynamics demonstrated a roughly quadrupling of volume at first contraction. Based on long-term follow-up, the 3-year actuarial estimate for treatment failure was 32.4%.⁴⁷

The effectiveness of SNM for urgency/frequency was evaluated in a later multicenter trial that randomized 51 patients after a successful test stimulation to either immediate InterStim (Medtronic, Minneapolis, MN, USA) implantation or a control group. In the treatment group, 56% of patients achieved either a 50% reduction in symptoms or achieved fewer than 7 voids per day; 8% of patients had no improvement in voiding symptoms at all. After 6 months, voiding diary, quality of life, and urodynamic parameters were significantly improved on average in the implant group versus no improvement in the control group. After 6 months of therapy, the neurostimulator was turned off and symptoms returned to baseline.⁴⁸

Older age and the presence of comorbidities appear to decrease the rate of treatment success with SNM. This was evaluated in one study involving 105 patients, including those with known neurologic conditions. Patients older than 75 years had a 30% symptom response rate. In comparison, 80% of patients younger than 45 responded to SNM. No patients with 3 or more comorbidities had complete resolution of symptoms.⁴⁹ Similarly, patients with pelvic pain or neuropathy may be more likely to fail SNM. A case series of patients failing SNM found that pudendal neuropathy was common, and that many patients benefited from a pudendal nerve block.⁵⁰

Percutaneous Tibial Nerve Stimulation

An early, uncontrolled observational study demonstrated objective urodynamic reduction in detrusor overactivity in 44 patients with OAB.⁵¹ More recently, 3 randomized controlled trials have assessed the efficacy of PTNS. In the Study of Urgent PC vs Sham Effectiveness in Treatment of Overactive Bladder Symptoms (SUmIT) trial, 220 patients with OAB were randomized to receive either PTNS or a sham therapy. Patients did not

use pharmacotherapy during the course of the trial. PTNS or a validated sham procedure was performed weekly for 30 minutes over 12 weeks. Outcomes were assessed using a voiding diary and global response assessment questionnaires at baseline and again 1 week after completing treatment. Compared with patients receiving sham therapy, patients who received PTNS had significant improvements in urinary frequency, urgency, urge incontinence episodes, and nocturia; 54.5% of patient receiving PTNS compared with 20.9% of patients receiving sham therapy reported moderate to marked improvements in global response assessment.¹²

These findings were confirmed in a European study randomizing 35 women with medication refractory OAB to either PTNS or placebo (electrical stimulation of the gastrocnemius muscle). In that study, 71% of patients receiving PTNS reported improvement compared with 0% in the placebo group.⁵² Both studies are important in that the placebo effect is well documented for patients with OAB⁵³ and demonstrates short-term efficacy of the procedure. Importantly, although these studies show improvement in symptoms with PTNS, the magnitude of the improvement is generally small and falls short of a “cure.”

In the Overactive Bladder Innovative Therapy trial, 100 patients were randomized to either 12 weeks of PTNS without pharmacotherapy or tolterodine extended release 4 mg. A global response assessment demonstrated significantly more patients reporting substantial improvement with PTNS compared with tolterodine (79.5% vs 54.8%). However, both treatments led to similar objective improvements in terms of urinary frequency and urge incontinence episodes, leading the investigators to conclude that PTNS offers similar efficacy as tolterodine.¹³

Longer-term observational studies have suggesting a durable response for at least some patients who respond to PTNS. Fifty patients who had responded to 12 weekly PTNS treatments as part of the SUmIT trial were enrolled in a continuing observational study. After 14 weeks of no treatment, patients received approximately 1 treatment a month. Only 1 patient had an adverse event, which was mild bleeding from the needle site. Only 29 of the 50 patients remained in the study after 3 years of follow-up with an estimated 77% maintaining moderate or marked improvement over this period.¹⁴

Overall, PTNS appears to be an effective treatment for patients with OAB, noting that, in published PTNS trials, only one exclusively involved patients who were nonresponsive to pharmacotherapy. PTNS appears to improve symptoms for

most patients similarly to tolterodine; however, few patients are cured or achieve complete relief of symptoms. There do not seem to be any significant adverse events associated with treatment. The treatment effect appears to be durable with monthly “maintenance” procedures, at least for some patients.

COST CONSIDERATIONS

SNM is associated with high initial treatment costs because of device costs, costs related to the test procedure, and OR and anesthesia costs for implantation. SNM must have excellent long-term efficacy to justify initial costs, estimated at \$22,226 in 2010.⁵⁴ In theory, an office-based test procedure may be useful in identifying patients who are likely to fail implantation. The office-based test procedure is less expensive than an OR procedure with permanent leads³⁹; however, permanent lead placement may be a more sensitive screening method for SNM.³⁶ Cost-effectiveness modeling studies have not yet demonstrated the cost-effectiveness of either test procedure.⁵⁵

Although no head-to-head trials have been performed, overall success rates are similar for PTNS and an SNM test stimulation. A recent Markov cost-effectiveness study used estimated success rates as 67% for PTNE versus 55.4% for an SNM test stimulation. Based on 2013 reimbursement rates, initial costs are also similar for the 2 treatments (\$1857 for SNM vs \$1773 for PTNS). A slightly higher percentage (90% vs 71%) remained on therapy with SNM versus PTNS after a successful initial treatment, but at a significantly higher cost (\$24,342 vs \$4867).⁵⁶

SUMMARY

OAB affects many, with profound effects on quality of life with high economic costs. Although antimuscarinic drugs can reduce voiding symptoms, many patients do not tolerate the side effects, and some do not experience sufficient relief. Modulation of bladder reflex pathways with office-based procedures, such as SNM and PTNS, have proven to be efficacious. They are minimally invasive and are important options in the treatment armamentarium for patients with OAB.

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Infusion Therapy and Implantables for the Urologist

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KEYWORDS

• Urology • Infusion • Treatment • Therapy • Implantables

KEY POINTS

- Urology has historically adapted to the changing health care environment.
- The urology practice is in the position to deliver many novel and unique therapies across multiple disease states.
- Urologists have been quick to adopt new technology, therapeutics, and devices to deliver state-of-the-art patient care with improved clinical outcomes.
- As urologists move toward less invasive, outpatient-friendly procedures, it is incumbent on the specialty that urologists offer comprehensive care to patients.

Historically, the practicing urologist has received classic surgical training. This has usually involved 1 to 2 years of general surgery and 3 to 4 years of urology residency, often times with a research component. The amount of out patient clinical experience may vary by program, with most educational instruction being based within the operating room. When a chief resident matriculates into clinical practice, he or she may spend upward of 50% of the time in the clinic setting. Urology represents a hybrid specialty, where most patients seen are symptom driven and may not have a defined diagnosis. There is a cognitive requirement to properly evaluate and determine an appropriate treatment plan for every patient, pending the result of the work-up. Currently, depending on the number of providers in the practice, geographic area, and scope of practice, accounting for some of the variables, the revenues generated from the nonsurgical portion of a practice may range from 30% to 65% of collections.¹

Medicine, in general, is changing rapidly. Most practices are faced with continued decreases in

reimbursement, rising group overhead, and sweeping health insurance reform at the federal level that threatens the very existence of independent community practice. The field of urology has been morphing with regard to its historical clinical and practice patterns. The pharmaceutical management of benign prostatic hyperplasia has reduced the number of surgical interventions.² The advent of minimally and noninvasive procedures continues to grow and the number of “open cases” is diminishing in training programs and in practice. There is an increasing amount of time now required for office therapeutics, because many of the treatments that have evolved can be delivered and administered in an outpatient setting. The busy urology practice is now in the position to deliver many novel and unique therapies across multiple disease states. As a result, clinicians can provide state-of-the-art care in a clinic setting and potentially reduce the overall costs of health care delivery. This article reviews some of these potential new opportunities available to the practicing urologist.

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HORMONE-REPLACEMENT THERAPY

As the life expectancy in the United States has significantly increased over the past century, men have increasingly encountered hypogonadism as they age. The Nobel Prize was awarded to Bute-nandt and Ruzicka in 1939 for their work in isolating testosterone. In men, testosterone is produced primarily by the testes with smaller amounts produced by the adrenal glands. Testosterone is converted to dihydrotestosterone by 5α -reductase and within androgen target cells. About 98% of circulating testosterone is bound, of this approximately 30% is bound to sex hormone-binding globulin and the rest is bound to albumin and other serum proteins; the remainder represents free testosterone. Bio-available testosterone is made up by free testosterone and that which is bound to albumin.³

There are several different assays used for measuring testosterone with different normal ranges for each. Measuring testosterone levels is not an exact science because circulating testosterone levels can be affected by many factors including medical conditions, diurnal variation, changes in SHBG, age, body mass index, and more. The definition of hypogonadism is controversial and to this point the American Urological Association released a white paper titled "The Laboratory Diagnosis of Testosterone Deficiency" in 2013. The position statement at the end of this document is as follows:

Based on the extensive review of published data and input from professional organizations, the members of this panel believe that, for now, diagnosis of hypogonadism should be based as much on the presence of signs and symptoms as on serum T measurement. Based on overall poor quality of T testing in most clinical laboratories and age bias of published reference ranges, no patient should be denied coverage for treatment based solely on payer defined cut-off points if need for such treatment is established by a health professional. The AUA works closely with regulatory and professional agencies to improve assay performance and normal range, and as literature accumulates, this position will be reevaluated.

Symptoms of hypogonadism include decreased libido, fatigue, erectile dysfunction (ED), decreased muscle mass, irritability, decreased motivation, and hot flashes. Men are becoming increasingly aware of hypogonadism as a diagnosis and of treatment options for this condition. This is caused in part by increased advertising in many communities by nonurologic practitioners.

Testosterone replacement can be administered in several different forms. Oral preparations are available but are rarely used in the United States because much of the drug undergoes first-pass metabolism by the liver and carries with it a higher incidence of primary hepatoma.³ Testosterone can be administered by intramuscular injections and there are different formulations for this available. Testosterone cypionate injection is available in two strengths: 100 and 200 mg/mL. The half-life of testosterone cypionate is approximately 8 days. Ninety percent of a dose is excreted in the urine, 6% in the feces, and inactivation of testosterone occurs mostly in the liver. Testosterone cypionate, 100 and 200 mg/mL, is manufactured in 10-mL multidose vials. Intramuscular (IM) injections of testosterone cypionate should be administered in the gluteus. Dosing varies based on patient's symptoms and serum testosterone levels. In general, 50 to 400 mg can be administered every 2 to 4 weeks for testosterone replacement in hypogonadal men.

Testosterone can also be applied topically. Testosterone gels available include Androgel, Testim, Fortesta, and Axiron. In addition, there is the once daily transdermal patch (Androderm). Testopel is a testosterone pellet, manufactured by Slate pharmaceuticals, that is implanted into the subcutaneous (SC) fat in the outer quadrant of the hip. This requires a short procedure in the clinic every 3 to 6 months. Each pellet contains 75 mg of testosterone.

There are several contraindications for use of testosterone replacement common to all methods and formulations of replacement therapy, including allergy or hypersensitivity to the drug; males with breast cancer; history or suspicion of prostate cancer; women who are or may become pregnant; and patients with serious cardiac, hepatic, or renal disease.

Men receiving replacement testosterone therapy should have hemoglobin/hematocrit checked periodically given the risk of polycythemia. Lipid panels should be checked regularly because of risk of hyperlipidemia while on replacement therapy and serum testosterone levels should be checked to assess efficacy of treatment. Baseline complete blood count and lipid panel should be checked before initiating testosterone-replacement therapy.

ERECTILE DYSFUNCTION

The incidence of ED increases with age and the prevalence of ED has increased in the United States alongside increasing life expectancies. In the Massachusetts Male Aging Study, which

surveyed men between 40 and 70 years of age in the Boston area, Feldman and colleagues⁴ demonstrated a 52% prevalence of ED and that the prevalence of complete ED increased from 5% to 15% between subject ages 40 and 70 years old. In their analysis of the US adult male population, Selvin and colleagues⁵ found the overall prevalence of ED in men greater than or equal to 20 years of age at 18.4%, with prevalence positively related to age, hypertension, cardiovascular risk factors, diabetes, and lack of physical activity.

The most important component of evaluation of a patient with ED is a thorough history and physical examination. Evaluation often includes the use of questionnaires, examples of which include the International Index of Erectile Function, the Erectile Dysfunction Inventory for Treatment Satisfaction, and the Brief Males Sexual Function Inventory.⁶⁻⁸ These questionnaires are also often used to monitor patient response to treatment.

Nonsurgical interventions for ED include lifestyle changes, pelvic floor muscle therapy, oral PDE5-inhibitor therapy, and use of a vacuum-erection device.^{9,10} Dr Giles Brindley, famous for presentation of his research results at the 1983 American Urological Association annual meeting, demonstrated the success of intracavernosal injection of phenoxybenzamine.¹¹ Options for intracavernosal injection therapy include papaverine; alprostadil; papaverine + phentolamine (Bi-Mix); and papaverine + phentolamine + alprostadil (Tri-Mix). Initiation of therapy with intracavernosal injection requires initial administration in clinic for patient education and to ascertain the effective dosing.

ADVANCED PROSTATE CANCER Androgen-Deprivation Therapy

In 1966, Charles Huggins received the Nobel Prize for Physiology and Medicine for his work in discovering the hormonal control of prostate cancer growth.¹² His work ultimately led to the development of androgen-deprivation therapy (ADT). Before the advent of pharmacologic castration, bilateral orchiectomy had been the gold standard for androgen deprivation because the testes produce 90% to 95% of testosterone.

Luteinizing Hormone-Releasing Hormone Agonists

Luteinizing hormone-releasing hormone (LHRH) agonist therapy was first administered for the treatment of prostate cancer in 1980. LHRH agonists work by stimulating the LHRH receptors in the pituitary gland to cause increased secretion of LH and follicle-stimulating hormone (FSH),

initially causing an increased production of testosterone. Continued LHRH agonism causes subsequent decreased LH/FSH production and hence decreased levels of testosterone result. The initial rise in testosterone can cause a flare response in patients with advanced prostate cancer. Antandrogens can be administered before initiation of LHRH agonist therapy to prevent a flare response. LHRH agonists include the following:

Lupron (leuprolide acetate)

- 7.5 mg IM q month
- 22.5 mg IM q 3 months
- 30 mg IM q 4 months
- 45 mg IM q 6 months

Eligard (leuprolide acetate)

- 7.5 mg SC q month
- 22.5 mg SC q 3 months
- 30 mg SC q 4 months
- 45 mg SC q 6 months

Viadur (leuprolide acetate): 65-mg implant placed SC in the inner aspect of the upper arm q 12 months. The implant must be removed at the end of the 12 months. This was removed from the market by the manufacturer (Bayer).

Vantas (histrelin): 50-mg implant placed SC in the inner aspect of the upper arm q 12 months. The implant must be removed at the end of the 12 months.

Zoladex (goserelin acetate)

- 3.6 mg SC q month
- 10.8 mg SC q 3 months

Trelstar (triptorelin)

- 3.75 mg IM q month
- 11.25 mg IM q 3 months
- 22.5 mg IM q 6 months

Gonadotropin-Releasing Hormone Antagonists

Gonadotropin-releasing hormone antagonists reduce the secretion of LH, FSH, and testosterone by blocking the gonadotropin-releasing hormone receptors in the pituitary gland. There is no flare response associated with gonadotropin-releasing hormone antagonist therapy. Firmagon (Degarelix), an initial dose of 240 mg SC (2 × 120 mg injections), is administered in the abdomen and then an 80-mg SC injection is given every 28 days going forward. Ninety-six percent of men have castrate levels of testosterone by Day 3, and 99% by Day 7.

Additional ADTs available but not necessarily administered in clinic include estrogens (diethylstilbestrol, Premarin, estradiol); progestins (Megace); antiandrogens (flutamide, nilutamide, bicalutamide); and androgen synthesis inhibitors (ketoconazole, aminoglutethimide).

There has been debate as to the optimal use of androgen deprivation for the treatment of advanced prostate cancer and much of this has to do with the potential side effects of therapy. Long-term androgen deprivation can lead to increased risk of cardiovascular events, diabetes, hyperlipidemia, anemia, osteoporosis, and fatigue. The benefit of long-term androgen deprivation for prostate cancer treatment must be weighed against the risk of increased risk of death from other causes and this requires individual assessment of each patient. To mitigate some of these risks, many practitioners advocate the use of intermittent ADT.

Provenge

Provenge (sipuleucel-T) is an immunotherapy approved by the Food and Drug Administration (FDA) for the treatment of men with asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer. Provenge is the result of culturing a patient's own antigen-presenting cells with the recombinant antigen PAP-GM-CSF. When administered to the patient, Provenge potentiates the patient's T cells to attack prostate cancer cells.

Treatment with Provenge starts with patients undergoing leukopheresis at an approved blood collection center. The result of the collection is then sent to a Provenge manufacturing facility, which then cultures the patient's immune cells with the recombinant antigen. Provenge is administered by peripheral or central intravenous (IV) access during a 1-hour infusion, usually 2 to 3 days after the leukopheresis. Approximately 30 minutes before initiation of infusion, patients are pretreated with acetaminophen and an antihistamine to reduce risk of an infusion reaction.

The IMPACT trial, a phase 3, randomized, double-blind, multicenter, controlled trial of 512 men with asymptomatic or minimally symptomatic castrate-resistant prostate cancer, demonstrated a 4.1-month improvement in overall survival at 24 months after treatment.³ The most common side effects experienced by patients receiving Provenge include fatigue, fever, chills, nausea, headache, and joint pain.

Xofigo (Radium-223 Dichloride)

Xofigo (radium-223 dichloride, formerly known as Alfaradin) is an IV-administered radiopharmaceutical that targets bone metastases with alpha radiation from radium-223 decay. A phase III study of radium-223 dichloride in patients with symptomatic hormone-refractory prostate cancer with skeletal metastases is ongoing with estimated completion date of December, 2013. Preliminary

results have demonstrated improved overall survival and increased time to first skeletal-related event (SRE).¹³

Radium-223 has been the first radiopharmaceutical to demonstrate increased overall survival and it was approved by the FDA in May of 2013 for the treatment of men with castrate-resistant prostate cancer and symptomatic bone metastases, and no known visceral metastases.¹⁴ The dose of Xofigo is 50 kBq per kilogram bodyweight and it is injected intravenously once every 4 weeks for a total of six injections. Radium-223 is usually administered by a radiation oncologist or nuclear medicine radiologist.

There are some urologists that will manage the infusion of chemotherapy, such as docetaxel and cabazitaxel, for advanced prostate cancer. The number of urologic providers administering such therapy might increase with time as comfort grows with administering systemic therapies, because this is a dynamic and growing area in urology.

BENIGN PROSTATIC HYPERPLASIA THERAPIES

The gold standard for traditional treatment of benign prostatic hyperplasia has been transurethral resection of the prostate. Since the advent of medical therapy in the mid-1980s, including α -adrenergic blockers and 5 α -reductase inhibitors, there has been an ever increasing movement toward medical therapy and minimally invasive procedures.²

Transurethral Microwave Thermotherapy

Transurethral microwave thermotherapy involves the placement of a specially designed catheter, containing a microwave coil, within the urethra. After the catheter is properly in place it is connected to the energy source and the prostate is treated. During treatment cooling fluid is cycled through the catheter to reduce risk of thermal injury to surrounding urethral tissue. This can be done with conscious sedation and local anesthesia in the office or outpatient setting.

Transurethral Needle Ablation of Prostate

The transurethral needle ablation of prostate catheter used for treatment includes a fiberoptic scope that allows for visual guidance of needle placement. The generator produces low-level monopolar radiofrequency waves that generate temperatures up to 100°C in the tissue around the needles. Depending on the practice of the urologist, this procedure can be performed in the clinic or in an operating room setting. The patient is placed in the dorsal lithotomy position with a

grounding pad placed over the sacrum. Anesthesia options include from local with lidocaine jelly, conscious IV sedation, to general sedation.

INJECTABLE THERAPIES FOR INCONTINENCE ***Intradetrusor Injection of Botulinum Toxin***

Injectable agents for the treatment of overactive bladder (OAB) remain limited; however, recent data for one injectable therapy, botulinum toxin, demonstrate exceptionally promising results. Botulinum toxin, previously approved by the FDA for the treatment of neurogenic detrusor overactivity, has recently gained indication for medication refractory OAB. Clinically, botulinum toxin is expected to gain rapid acceptance as a therapy for severe OAB, which has been refractory to standard management.

A potent neurotoxin, botulinum toxin is derived from anaerobic bacterium *Clostridium botulinum*. Although several structural serotypes have been identified (A–G), types A and B are the primary serotypes with clinical significance. Type A is the most common subtype used because of duration of effect when compared with type B.³ Botulinum toxin induces detrusor muscle relaxation by inhibiting the release of acetylcholine from the presynaptic nerve terminal. It is postulated that symptomatic relief is experienced because of reduction/suppression of involuntary detrusor contractions, leading to a reduction in many of the symptoms of OAB. Studies continue to investigate the action of botulinum toxin in more detail, including the possible contribution of afferent signaling in the urothelium leading to sensory suppression. For example, there may be an action on afferent C-fibers, which are postulated to contribute to the mechanism underlying the reduction of urgency.^{15,16}

Evolving literature provides robust evidence that intradetrusor injection of onabotulinum toxin A is effective, well tolerated, and safe.³ A clinical response may be seen in up to 60% of the women who receive botulinum toxin,¹⁷ although the duration of effect has been reported to vary widely because of variation in dosage and outcome measures.³ Benefits usually last between 3 and 12 months depending on indication and dosage.^{17,18} Studies have concluded that injection of botulinum toxin results in a significant increase in maximum cystometric capacity.^{19,20}

Preoperatively, patients must be able and willing to return for postvoid residual evaluations and have the ability to perform self-catheterization. In addition, patients should also be counseled that the effects of intradetrusor botulinum toxin diminishes over time, thus requiring repeat injections. Postoperatively, patients should be monitored

closely for transient urinary retention and urinary tract infections.⁷

Botulinum toxin can be injected into the bladder wall using either a rigid or flexible cystoscope and is often done as an outpatient procedure, using general, spinal, or local anesthesia. Multiple injection needles are commercially available and the intricacies of the procedure are outside the scope of this review. Ultimately, the botulinum toxin is injected into the detrusor muscle at multiple sites (generally 10–30 sites), avoiding the trigone because of a theoretical risk of vesicoureteral reflux. Interestingly, some studies suggest that suburothelial injections may have comparable efficacy to intradetrusor injections.³

Much attention has been given to what dose safely balances the symptomatic benefits with the postvoid residual urine volume related safety profile for use in medication-refractory OAB. In regards to botulinum toxin, less may prove to be more. Lower doses of botulinum toxin (100–150 U) have been shown to have beneficial effects, and larger doses (300 U), although they may be more effective and longer lasting, have more side effects, such as urinary retention, particularly in the neurogenic population.³ Indeed, depending on indication, a lower dose of 100 U may have comparable efficacy and improved safety over 200- and 300-U dosages.¹⁸ Doses of 100 U have demonstrated durable efficacy in the management of idiopathic OAB and urinary urgency incontinence.^{21,22}

Injectable Therapies for the Treatment of Stress Urinary Incontinence

Injectable agents for the treatment of stress urinary incontinence (SUI) represent a commonly used and minimally invasive therapeutic option. Although injectable agents for incontinence have been used for more than 100 years, their diminished success rate when compared with open procedures has often dampened enthusiasm as a durable treatment.²³ Therefore, injectable therapies are usually reserved as second-line treatment options or for women who prefer less invasive procedures or are more medically suited for them.²⁴

In addition to a second-line treatment option, other possible indications include elderly patients, patients with high anesthetic risks, patients who must remain on anticoagulants at all times, women who are young and desire more children in the future, or have mild persistent SUI after an incontinence procedure.^{25–27} Careful patient selection is important to the success of bulking therapies. Patients should ideally have urethral hypermobility of less than 30 degrees and have adequate urethral mucosal blood supply (and estrogen effects).²⁸

Literature suggests that efficacy and duration are inferior to surgery and patients are often appropriately counseled that injectable therapies may offer an improvement rather than a cure for their SUI symptoms.^{24,29} Patients should be advised that injection therapy is a process and not a one-time procedure; sometimes two or three injections (4 weeks apart) are required to achieve continence; and that periodic repeat injections may be necessary to maintain continence.²⁷ Active urinary tract infection, hypersensitivity to the injectable material, and presence of urethral diverticula are the major contraindications.

Ideally, a urethral bulking agent should be biocompatible, durable, cost effective, and nonimmunogenic, but despite enormous medical advances, the perfect bulking agent remains elusive.¹⁵ Clinical concerns regarding long-term efficacy, cost effectiveness, and patient safety remain a persistent challenge.²³ In general, glutaraldehyde cross-linked bovine collagen (Contigen) is the biomaterial most commonly injected worldwide with a cure rate of up to 53%.²⁹ More recently, a study from Europe has demonstrated that polyacrylamide hydrogel (Bulkamid) resulted in a subjective response rate (cured or improved) of 64% and a significant decrease in urine leakage after 24 months.³⁰ Patients should be counseled that limited data exist with which to assess the long-term safety and efficacy of injectable agents.³¹ Multiple additional agents are commonly used and are gaining traction for women wishing to avoid surgical interventions. Currently available injectable agents for SUI include glutaraldehyde cross-linked bovine collagen (Contigen); carbon beads (Durasphere); silicone particles (Macroplastique); and calcium hydroxyapatite (Coaptite). New agents undergoing development include polyacrylamide hydrogel (Bulkamid), autologous chondrocytes, and autologous muscle-derived cells.

Depending on the injected material used, the goal is not to coapt the urethral mucosa but to obtain "static increase in resistance in the urethral outlet" and thus avoid overinjection.²⁸ The agent can be either injected periurethral or transurethral, such that the agent is adequately injected into the bladder neck or proximal urethra, preferably into the submucosa or lamina propria. Different injection sites can be used, such as the 3- and 9-o'clock position or the 4- and 8-o'clock position.³² Risks generally include urinary retention, urinary tract infection, hematuria, and transient dysuria. Although urethral bulking agents have a lower cure rate than open surgery, they are generally associated with fewer complications.

BONE-TARGETING THERAPY

Since the Nobel Prize winning discovery by Huggins and Hodges of the role of circulating androgens in patients with prostate cancer,¹² ADT remains the mainstay of advancing prostate cancer in patients with metastatic and nonmetastatic disease. As many as 200,000 patients in 2008, both Medicare and commercially insured, received ADT for greater than 6 months.^{33,34} However, it has long been recognized that one of the potentially serious and undertreated complications of ADT is bone mineral density loss (BMD). It has been estimated that BMD loss in men on ADT may be as high as 4% per year once therapy has been instituted.³⁵ Contrast this with the recognized loss in the postmenopausal woman, which is commonly reported and treated, of 1.5% to 2%.³⁶ This is an underrecognized medical problem that the urology community needs to address.

Normal bone turnover is a coordinated dance between osteoblasts and osteoclasts, resulting in formation and resorption, mediated by receptor activator of nuclear factor kappa (RANK) ligand.³⁷ It is thought that estrogens have a protective effect by increasing osteoblast proliferation (increased bone formation) and decreasing RANK ligand production by the cells (decrease resorption).³⁸ When ADT is initiated, the lowering of serum testosterone, which is peripherally converted to estrogen by aromatase, results in lowering of peripheral estrogen levels and results in decreasing osteoblast production and increased RANK ligand activity, favoring resorption over formation with resultant BMD loss and increased risk to male osteoporosis.³⁷ This castration treatment-induced bone loss (CTIBL) in the patient with nonmetastatic prostate cancer is associated with a 45% excess risk of fracture compared with patients not on ADT.³⁹ This increased fracture rate results in a higher mortality, especially if the patient requires hospitalization.⁴⁰

A National Comprehensive Cancer Network Task Force Report in 2009 emphasized the need for bone health management in cancer care.⁴¹ Strategic to this push to preserve BMD and decrease fracture risk is supplemental calcium, vitamin D, lifestyle modification, and pharmacologic therapy. Oral bisphosphonates (alendronate, ibandronate) are pyrophosphate analogs that are directly taken up by the osteoclasts, which results in decreased bone resorption and may have an apoptotic effect.⁴² However, bisphosphonate therapy is not approved for CTIBL.

In September of 2012, the FDA approved denosumab, a fully human monoclonal antibody that binds RANK ligand, which results in a decrease

in bone resorption, a 6.7% increase in BMD at the lumbar spine at 2 years, and a reduction in new vertebral fractures compared with placebo.⁴³ The dose is 60 mg SC every 6 months with an increase risk of hypocalcemia, arthralgia, back pain, osteonecrosis of the jaw, and cataracts.⁴⁴ This dose is packaged and marketed as Prolia (Amgen) and is indicated for patients with nonmetastatic prostate cancer on high-risk drug (ADT) for the prevention of CTIBL.

Patients that unfortunately progress despite being on ADT and develop castration-resistant prostate cancer (CRPC) with bone metastasis are at an increased risk of developing SRE, defined as a patient that requires palliative radiation to the bone for pain control and surgical stabilization for a fracture, and that experiences a pathologic fracture or spinal cord compression.⁴⁵ An SRE can be a devastating event, altering quality of life in patients with already limited survival.³ Zoledronic acid (ZA), an intravenous bisphosphonate, has been approved in the patient with CRPC for SRE prevention. It delayed SRE by a median time of 17.1 months, compared with the control arm, which may have included patients on supplemental calcium and vitamin D, at 10.7 months.⁴⁵ Many urologists, however, were reluctant to administer ZA in the office because it required a 1-hour infusion and monitoring of renal function. The former was not necessarily what most offices were or are set up to do, unlike medical oncology clinicians, and many patients went untreated.

In November of 2010, XGEVA (Amgen) was approved for the prevention of SRE in patients with bone metastasis from any malignancy except multiple myeloma.⁴⁶ XGEVA is the same molecule as Prolia, denosumab, but at a SC dose of 120 mg monthly. It was shown to be superior to ZA in a head-to-head study for the prevention of first and subsequent SRE with an 18% risk reduction compared with ZA. The median time to the first SRE was 20.7 months. Because of denosumab's SC route of delivery, it can and should be incorporated into the typical urology practice. The National Comprehensive Cancer Network recommends bone targeting therapy for patients with CRPC.⁴⁷

SUMMARY

The specialty of urology has historically adapted to the changing health care environment. It has been quick to adopt new technology and new therapeutics and devices to render state-of-the-art patient care with improved clinical outcomes. As the field moves toward less invasive procedures that are outpatient friendly, it is incumbent on the specialty,

especially within the potentially changing reimbursement environment, that clinicians offer comprehensive care to patients.

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Coding for Urologic Office Procedures

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KEYWORDS

- Coding and reimbursement • Urology office procedures • Urology CPT codes
- Coding for office procedures

KEY POINTS

- The American Medical Association is the steward of Current Procedural Terminology (CPT), and the Centers for Medicare and Medicaid Services (CMS) often implements that terminology in rules and regulations that are followed by most insurance payers.
- CPT codes are highly specific, and there is a code or set of codes to fit all office urology procedures and common scenarios.
- Many resources are available to assist in complex coding scenarios.
- Coding for urologic office procedures is founded in proper documentation in the medical record.
- Urologic office procedures often involve expensive drugs or disposables, and recovery of acquisition costs depends on a detailed understanding of coding rules and nuances.

INTRODUCTION AND PURPOSE

Typical urologists today generate a significant portion of practice revenue performing procedures in the office, and a detailed knowledge of documentation and coding guidelines is necessary to insure appropriate, compliant, and optimal reimbursement. Several recent trends have highlighted the importance of coding, billing, and collecting payment correctly for office-based procedures. Diagnostic and therapeutic procedures, once commonly requiring facility-based anesthesia services, can now be performed in a urologist's office. The stewards of procedural terminology have introduced more codes with more specificity to replace general codes in the urinary and male genital sections and, in some cases, deleted once

commonly used codes. Advances in technology have introduced new office-based procedures into the armamentarium of urologists—for example, in the treatment of benign prostatic hyper trophy—demanding new codes. Worker salaries and other practice expenses for urologists continue to rise, while allowable charges for procedures have remained flat or even decreased. Employers and insurance companies are asking patients to shoulder more responsibility for health care expenses; patients in turn are demanding more transparency in their bills. The emergence of value-based payment systems and the passage of health care reform legislation are predicted to result in savings primarily by reducing payments to hospitals and surgical specialists. Commercial

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Disclaimer: Best efforts to provide accurate information, codes, and descriptions have been made in development of this information. Rules and regulations are subject to interpretation and change, however. Variation by payer, region, and contract are common. Advice and direction on coding and reimbursement are based primarily on Medicare rules with general advice for private payers included where relevant.

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payers are attempting to control rising costs by managing utilization of high cost procedures, thereby increasing the number of office-based procedures that require preauthorization. Finally, federal agencies have signaled their interest in recovering overpayments made to providers for high-volume, high-cost procedures with an emphasis on medical necessity and appropriate documentation. In this complex and changing landscape, it is imperative that urologists document and bill correctly for office procedures.

This article first reviews some general principles of proper documentation, coding, and getting paid for procedures performed in a urologist's office. Then, specific coding and billing issues for each of the most common diagnostic and therapeutic procedures are examined. By the end of this article, readers should have a tool for their practice that should optimize reimbursement and ensure standard and compliant documentation and coding.

GENERAL PRINCIPLES

Definition of a Procedure

Although many factors may determine the setting in which a procedure is performed, for the purposes of this article, office-based urologic procedures are defined as those urinary or genital tract procedures that do not require services only available in an operating room and that are commonly performed in a urologic office setting in the United States. The procedure may be diagnostic or therapeutic in nature, may be invasive or noninvasive, and usually includes the professional service to perform the procedure, any same-day evaluation and management (E&M) services related to the procedure, and the supplies necessary to conduct the procedure. Most office-based urologic procedure codes and their descriptions can be located in the surgery section of the American Medical Association CPT manual, urinary system subsection (50010-53899) or male genital subsection (54000-55899).¹

Documentation

Proper documentation of office procedures is at the foundation of good clinical care, licensure in most states, risk management, compliant coding, and optimal reimbursement. All urologists should be familiar with an axiom used by utilization review companies, payers, state and federal regulators, and malpractice experts and quoted in the American Medical Association CPT manual: "if something is not documented in the medical record, then the procedure was not performed and therefore is not subject to reimbursement." The

components of procedural documentation are standard, often routine, and lend themselves well to paper forms or electronic templates. The indication for the procedure should be clearly listed to support medical necessity. The place of service (office and examination room) should be clearly specified, not simply inferred from the name of a provider and a date. The normal and abnormal findings of the procedure, and any complications, should be described separately from the procedure itself because they are always unique to a patient and procedure. The procedure note itself should be descriptive enough to support the relevant procedure code and specific enough to support a standard of care but not contain unnecessary detail that obscures the important content. Finally, the procedure note should be separate and clearly distinguishable from documentation of any other services performed during the same visit.

Documenting common procedures presents an opportunity for efficiency by designing and using paper forms or electronic templates, but a careful balance must be struck between benefit and risk. With the adoption of electronic health records in group practices, the person who designs the templates is often not the only person who uses the templates; furthermore, many electronic medical records do not easily allow users to view the data entry screen and the output screen at the same time. Finally, the ability to "copy forward" procedural notes, such as surveillance cystoscopy for bladder cancer, can result in "cloned notes" and unintentionally perpetuate documentation that is not appropriate. These factors can introduce significant risk of inaccurate documentation that can be mitigated with careful template design. For example, a male cystoscopy template might contain default content for preparation of the genitals, insertion of the scope, and systematic inspection of the bladder—but should not contain text, settings, or other content, such as "all findings were normal," that could be inserted inappropriately and inadvertently. A well-designed template should allow users to be efficient, thorough, and accurate in the creation of a compliant yet readable note. The ideal procedure template should also make clear the contents of the note output to minimize inadvertent documentation.

Coding for Office-Based Procedures

Office procedures are described and classified in CPT 5-digit codes, a system copyrighted by the American Medical Association, mandated by federal law for government insurance programs, and accepted as the standard nomenclature by commercial insurance payers. The most relevant

codes in the CPT manual for office-based urology procedures are in the surgery subsections of urinary system (50010-53899) and male genital system (54000-55899).¹ The CPT codes are revised once a year, and it is essential that the urology practice keep current with additions, deletions, and changes to the CPT manual. Causes for claim denial include use of an outdated code, failure to use a new code, reporting the wrong code, and use of a nonspecific unlisted code when a specific one exists. Whenever possible, the provider or staff member performing the office procedure should be the same person who assigns or approves the code submitted for billing. Urologic procedures performed in an office setting should always be billed with the place of service code 11 (office facility).

Multiple procedures

Although CPT codes for most office-based urology procedures are specific and inclusive, some office procedures (transrectal ultrasound-guided prostate biopsy, for example) require more than 1 CPT code for compliant coding and optimal reimbursement. The rules governing which codes can be paired with other codes are administered by the CMS and are called the National Correct Coding Initiative (NCCI) (also known as CCI). This system was implemented in 1996 by the CMS “to promote national correct coding methodologies and to control improper coding leading to inappropriate payment. NCCI code pair edits are automated prepayment edits that prevent improper payment when certain codes are submitted together for Part B-covered services.”² For example, the NCCI edits permit submitting a prostate biopsy (55700) and a transrectal ultrasound (76872) but never allow the submission of cystoscopy (52000) and complex catheterization (51703) on the same date of service. Most commercial insurers include NCCI edits, and the CMS updates this list quarterly.

When multiple codes are necessary and appropriate, it is best practice to report the procedure with the highest fee first, the additional procedures on separate lines of the claim form with a -51 modifier attached, and to submit full fees for each procedure. Most insurance payers reduce the reimbursement of the second and additional procedures by at least 50%. The practice of itemizing multiple CPT codes when only 1 code is “needed” is referred to as “unbundling,” and systematic unbundling may invite the scrutiny of auditors and regulators. In some circumstances, it is appropriate to report multiple codes considered bundled under current CCI data sets—a modifier may be used when conditions warrant separate reporting

(decision for surgery, left or right laterality for example). Later in this article, the best practice for coding common procedures that require more than 1 CPT code is discussed.

Global period

In order to process claims quickly and accurately, most payers have developed specific definitions for a global surgical package, including time frames (the global period) during which other professional services are considered included in the payment of the procedure. Most payers follow the definition of the global surgical package developed by the CMS, and most procedural CPT codes on the Medicare fee schedule are associated with a global period of 0, 10, or 90 days. The global surgical package specifically includes the procedure itself, all services that are a “usual and necessary” part of the procedure, local anesthesia, the treatment of any minor complications related to the procedure, E&M services performed on the day of the procedure (exceptions discussed later), and, in cases of 90-day global packages services, the day of and day prior to the procedure. Diagnostic urology procedures performed in the office generally have a 0-day global period, but some therapeutic procedures—including vasectomy—have a 90-day global period. Urologists should also understand when it is permissible to bill for an office procedure when it is performed in the global period of another earlier procedure, such as cystoscopy and stent removal after extracorporeal shock wave lithotripsy. Submitting claims for services normally included during the global period is considered unbundling. The global period for each CPT code is generally listed on the insurance company fee schedule and can also be found at the CMS Web site.³

Supplies

CPT and Healthcare Common Procedure Coding System (HCPCS) level II codes also form the basis of the resource-based relative value system used by the CMS and most commercial payers to set fees. Most codes contain component relative value units that consider physician work, practice expense, and malpractice cost for that particular procedure. For this reason, the cost of supplies and equipment used during an office-based procedure are usually factored into the fee and are generally not billed or reimbursed separately.

Modifiers

A urologist’s coding staff should be familiar with CPT code modifiers. When used appropriately, modifiers may increase reimbursement and, when used inappropriately, may result in claim denial or payer audits. Although a comprehensive

discussion of modifiers is beyond the scope of this article, some examples of modifiers that might be appropriate for some office-based procedures are found in [Table 1](#).

Incident to Services

Office-based urology procedures may be performed under the supervision of a physician and, therefore, reimbursed under “incident to” rules. The CMS defines “incident to services” as those that are provided “as part of” a physician’s professional services in the office and directly supervised by the treating physician. To qualify as “incident to,” a service must be rendered to a patient who was initially seen by a treating physician, and the supervising provider must remain actively involved in the care of that patient; the supervising (billing) provider must be physically present in the facility and immediately available when the service was provided. Medical assistants, nurses, and others have long provided “incident to services” in a urology office: examples include injections, catheterizations, and measurement of residual urines. The increased presence of nurse practitioners (NPs) and physician assistants (PAs) in urology practices has created some confusion about “incident to” rules for several reasons:

- NPs and PAs are licensed professionals credentialed by insurance companies and may bill under their own identification (ID) number (including the CMS) for services performed independently. When doing so, physician extenders are generally reimbursed by the CMS at 85% of the fee schedule amount. These services are not billed “incident to.”

Table 1 Examples of CPT code modifiers	
22	Unusual procedural services (example, repeat vasectomy)
26	PC only (example, urodynamics interpretation)
51	Multiple procedures (example, transrectal ultrasound biopsy)
58	Related procedure during postoperative period (example, stent removal)
59	Distinct procedure
76	Repeat procedure by same physician
77	Repeat procedure by another physician
78	Unplanned return to the operating/ procedure room
79	Unrelated procedure during postoperative period

- NPs and PAs may also perform services “incident to” a physician service and, therefore, bill under a physician’s ID number. When doing so, the physician is reimbursed at 100% of the fee schedule amount.
- NPs and PAs enjoy a scope of practice broader than medical assistants and nurses and narrower than physicians, defined by a state licensing authority and subject to modification by a supervising physician of record (who is also licensed by the state).
- Private payers may allow “incident to” reporting for NPs and staff without a physician’s physical presence in the office

Subject to any limitations on the scope of practice imposed by state licensure, many urologists have trained NPs and PAs to perform routine procedures, including cystoscopy, prostate biopsy, and vasectomy under direct supervision in the office. In order to qualify under “incident to” rules, patients must have been seen for an initial evaluation by a supervising physician and the supervising physician must be physically present within the office suite while the procedure is performed by the employed extender. Assuming these conditions are met, claim forms are submitted just as if physicians themselves had performed the procedure. The increased volume of services performed when both a physician and an extender are billing under the physician provider ID number could invite auditing activity by payers, and records should be maintained (calendars and schedules) to prove that the physician was physically present in the office on the date of such claims.

Evaluation and Management Services

As described previously, the CMS and other payers consider the procedure CPT code inclusive of all visit charges for that day, and charges for E&M codes are generally not paid separately for the same date of service. CPT coding guidelines do provide for billing for an E&M service, as long as it is separate and distinct from the procedure itself. In these cases, the modifier, -25, is appended to the E&M service, not the procedure code. For example, a patient who travels a great distance for care may be scheduled for follow-up of bladder cancer and prostate cancer during the same visit. During that visit, the urologist may perform surveillance cystoscopy (for the bladder cancer) and separately perform a digital rectal examination, review recent prostate-specific antigen results, and schedule further testing for prostate cancer follow-up. The claim form should reflect 52000 linked to bladder cancer and the appropriate level E&M code with a -25 modifier linked to prostate

cancer. Coding guidelines do not require 2 separate diagnoses in order to bill a separate significant E&M service, but separate diagnoses help justify the additional service.

A related but separate scenario commonly occurs when a patient is seen primarily for an E&M service and a decision is made to perform an office-based procedure the same day. For example, a patient referred for the initial evaluation of gross hematuria may receive a recommendation to have cystoscopy the same day. In that scenario, the appropriate coding includes a 52000 and a modifier attached to the appropriate E&M code. This example highlights that the CMS frequently develops rules and definitions that differ from the CPT directives. CPT guides physicians to append the modifier, -57, to the E&M code in this circumstance because this modifier alerts payers that a decision for the procedure was made during the E&M service. Medicare, however, considers the decision for surgery part of the global surgical package for minor procedures (defined as procedures having a 0-day or 10-day global period); therefore, the modifier, -57, is not appropriate; because Medicare does allow for E&M services that are clearly separate and identifiable to be reported and paid on the same day as a minor procedure, the modifier, -25, is appropriate for this payer and others that follow Medicare policy.

Finally, as discussed previously, documenting procedures separate from any E&M services performed the same day help support correct coding and justify claims that are audited for any reason.

Laboratory and Radiology Services

Urology practices are increasingly performing their own laboratory and radiology services, and coding for these services requires a detailed understanding of the specific codes, the circumstances under which they can be billed, and the concept of professional component (PC), technical component (TC), and global service (PC and TC). Just as with other CPT codes, the description of the laboratory or radiology service is specific and it is crucial to match the service to the correct code.

Specimen collection

Physicians are permitted to bill and collect a fee for collecting blood via venipuncture and urine specimens via catheterization in addition to other services performed in the office. The proper codes for the CMS are G0001—routine venipuncture for collection of specimen(s) and P9612—catheterization for collection of specimen(s); most private payers use a different code for venipuncture 36415. A separate specimen collection fee cannot be charged for simple urines, swabs, or biopsies

(as it is considered included in the procedural code).

PC TC global

Pathology, radiology, urodynamic, and some other diagnostic services may be billed globally by urologists or split into PCs and TCs. For example, a urologist who performs a renal ultrasound in the office and renders the official interpretation bills 76775, and the provider is reimbursed for the equipment, supplies, and technical support as well as the interpretation of the results and the report. It is important when billing globally for a diagnostic study that the report is documented separately from any other services performed that day. A practice that owns an in-office pathology laboratory may bill for the TC (equipment, supplies, and labor) of preparing surgical pathology and prostate biopsy (88305-TC) and send the slides to an independent pathologist for interpretation; some practices contract with pathologists and bill globally. Finally, there may be some circumstances where a urologist performs only the professional interpretation of a test and another supplier bills for the TC; in those circumstances, the modifier, -26, should be appended (ie, urodynamics 51726-26).

Resources and Reference Materials

Coding for medical services is a complex and rapidly changing subject area and it is important that a urology practice performing procedures maintain current competency or expertise in this field. As discussed previously, the American Medical Association is the steward of the CPT manual.¹ Additions, deletions, and revisions are published in October and are effective January 1 of the following calendar year. The CPT manual is a reference work and general guide, but often the answers to coding and reimbursement questions are found in or from CMS manuals, local coverage determinations, subject matter experts in specialty societies, online forums, or even individual explanations of benefits that accompany payments for claims. The complexity of this field has created a demand for credentialed professionals, and organizations, like the American Academy of Professional Coders and the American Health Information Management Association, certify thousands of professional coders for careers in physician offices. The American Academy of Professional Coders offers a specialty certification in urology, the Certified Urology Coder, which is specifically designed for urologic procedures, ancillary procedures performed in the office, and other urology-specific scenarios. Many large urology practices employ such professionals to

optimize reimbursement and mitigate the risk of incorrect coding. In addition to these valuable resources, the American Urologic Association’s Office of Practice Management offers both free and purchased access to subject matter experts in urology coding.⁴

COMMON UROLOGY OFFICE PROCEDURES

In the following sections, common urology office procedures are described by groupings that generally reflect their common association. A description of the codes in each family is followed, when pertinent, by special considerations for documentation and best practices for using these codes.

Urinalysis Procedures

Documentation

The distinction between these 4 codes lies in whether an automated reader was used and whether microscopy was performed; therefore, the documentation should clearly state whether an automated reader was used and ideally incorporate the output from that automated reader. If microscopy is performed, the results should be documented separately from the other constituents and conform to a standard format (ie, red cells, white cells, crystals, bacteria, and other). Urinalysis is commonly performed as part of routine patient intake, and ideal documentation should clearly reflect an order associated with a clear indication (Table 2).

Post Void Residual Procedures

Documentation

Determining the amount of urine remaining in the bladder after a patient has voided is typically measured in a urology office with ultrasound or by inserting a catheter in the bladder and measuring the urine volume drained. Payment for these procedures has become a specific target of payers and

auditors, and the advent of noninvasive testing may have broadened the indications for urologists and their patients. Most payers do not reimburse for this procedure when it is only used as a screening tool. Office documentation should clearly address the indication for measurement of residual urine and state which method is used (including the size of the catheter, if used) (Table 3).

Coding best practice

CPT 51701 has a global period of 000, and billing of E&M services on the same date requires use of modifiers for the E&M service code. The 51701 is included in the NCCI listing for most urology service codes with an indicator that does not allow unbundling with a modifier. Therefore, it is not appropriate to report code 51701 for dates of service in which other urologic services are reported (for example, cystoscopy) (Table 4). Furthermore, the 51701 is considered a minor surgery and is included in the postoperative period of other surgical services.

Cystoscopy Procedures

Documentation

This closely related group of CPT codes underscores that the correct code can only be applied with the correct and specific description of the procedure performed; also, urologists may start the procedure intending to perform a simple diagnostic cystoscopy but based on findings perform a different closely related procedure/code. Many electronic medical record templates are built in a fashion to link templates to generation of specific CPT codes; in those cases, it is important to choose the template/begin the documentation after knowing the final code to be applied in order to avoid generating the wrong code. When performing biopsy, fulguration, or treatments, the exact number, size, and location of the lesions should be documented because this may determine the appropriate code. When removing a foreign body from the bladder, it is prudent to document whether or not the foreign body is intact or remnants remain.

Table 2 Urinalysis		
Code	Global	Description
81000	XXX	Urinalysis, nonautomated, with microscopy
81001	XXX	Urinalysis, automated, with microscopy
81002	XXX	Urinalysis, nonautomated, without microscopy
81003	XXX	Urinalysis, automated, without microscopy

Table 3 Post void residual		
Code	Global	Description
51798	XXX	Measurement of postvoiding residual urine by ultrasound, nonimaging
51701	000	Insertion of nonindwelling bladder catheter

Table 4
Cystoscopy procedures

Code	Global	Description
52000	000	Cystourethroscopy (separate procedure)
52001	000	Cystourethroscopy with irrigation and evacuation of multiple obstructing clots
52204	000	Cystourethroscopy, with biopsy(s)
52214	000	Cystourethroscopy, with fulguration (including cryosurgery or laser surgery) of trigone, bladder neck, prostatic fossa, urethra, or periurethral glands
52224	000	Cystourethroscopy, with fulguration (including cryosurgery or laser surgery) or treatment of MINOR (less than 0.5 cm) lesion(s) with or without biopsy
52281	000	Cystourethroscopy, with calibration and/or dilation of urethral stricture or stenosis, with or without meatotomy, with or without injection procedure for cystography, male or female
52287	000	Cystourethroscopy, with injection(s) for chemodenervation of the bladder (ie, botox)
52310	000	Cystourethroscopy, with removal of foreign body, calculus, or ureteral stent from urethra or bladder (separate procedure); simple

Coding best practice

These codes are generally bundled with the other codes in this list and usually cannot be billed together on the same date of service. For example, it is not appropriate to bill for a biopsy (52204) and fulguration (52224) of the base of the same site (Table 5). Coding of biopsy in conjunction with other services may be allowed with modifiers if the biopsies are taken from sites other than lesions sites being treated. Diagnostic cystoscopy may not include a discussion of treatment of the findings; therefore, an E&M code can be billed separately for that discussion (with the appropriate modifier) with some payers. Finally, cystoscopy with treatment of multiple lesions should be coded according to the method and size of the largest lesion.

Table 5
Transrectal ultrasound–guided biopsy of the prostate

Code	Global	Description
55700	000	Biopsy, prostate; needle or punch, single or multiple, any approach
76872	XXX	Ultrasound, transrectal
76942	XXX	Ultrasonic guidance for needle placement (eg, biopsy, aspiration, injection, localization device), imaging supervision and interpretation

Transrectal Ultrasound Guided Biopsy of the Prostate**Documentation**

Many urologists perform a diagnostic ultrasound at the same time as performance of a transrectal ultrasound–guided biopsy of the prostate. The documentation for the diagnostic ultrasound should include a description of the equipment and the technique, separate documentation of the findings, including the dimensions of the prostate, and an image of the prostate; the image serves as an important record of the technical portion of the radiology procedure and the findings constitute the PC/interpretation included in the global code. The biopsy procedure should be distinct from the diagnostic ultrasound in the office documentation and should include a description of the equipment used and the location of the biopsy sites. Although a statement that ultrasound guidance was used is prudent, no image is necessary to support the use of the code 76942.

Coding best practice

When billed together, the codes should be listed in the order shown and no modifiers are necessary; 55700 does have a 0 global, and appropriate modifiers should be attached to any additional services billed the same day. The concept of global period does not apply to radiology codes.

Vasectomy Procedures**Documentation**

If a vasectomy is performed on the same day as the consultation (E&M visit), it is critical to document the consultation and procedure separately (Table 6). Vasectomy is a high-volume routine office procedure and, as such, lends itself well to standard documentation templates. As discussed previously, this presents both opportunity for

Table 6 Vasectomy procedures		
Code	Global	Description
55250	090	Vasectomy, unilateral or bilateral (separate procedure), including postoperative semen examination(s)
55450	010	Ligation (percutaneous) of vas deferens, unilateral or bilateral (separate procedure)

efficiency if the procedure is routine and risk for inaccuracy if the procedure is not routine. By requiring separate documentation of the procedure and the findings, most mistakes can be avoided. It is important to document the method of occlusion and whether or not a segment of vas was removed during the procedure because there is more than 1 possible CPT code for vasectomy.

Coding best practice

There are 3 CPT codes for vasectomy, and they differ in 2 important respects. First, 1 code specifically refers to vasectomy, which the authors interpret to mean removal of a segment of vas. If a segment of vas is removed, the most appropriate code is 55250; if a ligation procedure is performed without removal of vas, then 55450 may be more appropriate. Second, 1 code has a 90-day global and the other a 10-day global period. If a decision to perform 55250 is made the day of (same-day consult) or the day prior to the procedure, it is necessary to append a -57 modifier to the E&M code. If a decision to perform 55450 is made the same day as the procedure, during the process of a separate significant identifiable E&M services, modifier -25 should be appended to the E&M code; otherwise, no modifiers are necessary. In summary, the date of the consultation and the type of the procedure performed are the key variables in determining which codes and which modifiers are best applied.

Bladder Catheterization, Irrigation and Instillation Procedures

Documentation

Catheterization of the bladder is a common urologic procedure with different indications, and one of the challenges in documentation is that it is often performed by nonphysicians (Table 7). The best documentation practices call for the provider who performs a procedure to be the provider

Table 7 Bladder catheterization and irrigation and instillation procedures		
Code	Global	Description
51102	000	Aspiration of bladder; with insertion of suprapubic catheter
51700	000	Bladder irrigation, simple, lavage and/or instillation
51701	000	Insertion of nonindwelling bladder catheter (eg, straight catheterization for residual urine)
51702	000	Insertion of temporary indwelling bladder catheter; simple (eg, Foley)
51703	000	Insertion of temporary indwelling bladder catheter; complicated (eg, altered anatomy, fractured catheter/balloon)
51705	000	Change of cystostomy tube; simple
51710	000	Change of cystostomy tube; complicated
51720	000	Bladder instillation of anticarcinogenic agent (including retention time)
P9612	000	Catheterization for collection of specimen, single patient, all places of service

who documents the procedure. Therefore, it is important to train ancillary staff in proper documentation to support this family of codes.

Documentation should include the indication for catheterization, the method used, the equipment used, and the findings (such as residual urine). A common scenario in a urology office is that a physician may become involved in catheterizing a patient after several failed attempts by staff; those failed attempts should be documented in addition to a successful attempt in order to support a higher level of complexity for the procedure. This pertains to urethral catheterization (51702 and 51703) and to catheterization through an established suprapubic tract (51705 and 51710).

Insertion of a nonindwelling catheter to determine postvoid residual (51701) or to obtain a specimen for testing (P9612, Medicare) requires only a brief description but should include the exact amount of urine obtained and, if pertinent to the indication, the appearance of the urine. When a temporary catheter is inserted for irrigation or instillation of various agents, a more complete description of

the indication, the findings, and patient tolerance is advised. Best practice calls for documenting dosage, lot number, expiration date, and even National Drug Code (NDC) for office-administered drugs and biologics. The administration procedure note should clearly explain whether the drug/biologic was acquired and provided by the physician office or by the patient (for example, a prescription or specialty pharmacy shipment).

Many urologists perform suprapubic trochar cystostomy in the office (51102). Appropriate documentation should include informed consent, the indication for the procedure (failed attempts at urethral catheterization, for example), the technique and equipment used, and the findings/results.

Coding best practice

Each of the codes in this family has a global period of 000 and, as such, any E&M services rendered separately on the same day require the appropriate modifiers (and documentation). These codes are bundled in to most office procedures and generally cannot be billed with those procedures (for example, cystoscopy 52000) or with each other unless a clear and separate indication is carefully documented.

Medications used during a catheterization procedure are billed using HCPCS code (for example, J codes) only if acquired and provided by the physician office and so documented. Many medications have different codes for different dosage/formulations with different reimbursement schedules, and careful attention to detail, supported by documentation, is necessary for optimal reimbursement.

The costs of the catheter, insertion kit, collection bag, and other supplies (except drugs) associated with this family of procedures are considered by most payers to be included in the payment for the procedure and, therefore, are not separately reported in most circumstances. Medicare allows for billing of catheters and leg bags supplied to patients for in-home use only if the billing entity has the appropriate supplier number and the supplies are provided to patients who are permanently incontinent.

Urodynamics Procedures

Documentation

The number of different procedures that constitute “office urodynamics” highlights the importance and application of principled documentation to support optimal coding and reimbursement (Table 8). The indication for and medical necessity of the procedure should be clearly documented. Like radiology services, the technical portion of the procedure may be performed on a different

Table 8
Urodynamics procedures

Code	Global	Description
51725	000	Simple cystometrogram (eg, spinal manometer)
51726	000	Complex cystometrogram (ie, calibrated electronic equipment)
51727	000	Complex cystometrogram (ie, calibrated electronic equipment); with urethral pressure profile studies (ie, urethral closure pressure profile), any technique
51728	000	Complex cystometrogram (ie, calibrated electronic equipment); with voiding pressure studies (ie, bladder voiding pressure), any technique
51729	000	Complex cystometrogram (ie, calibrated electronic equipment); with voiding pressure studies (ie, bladder voiding pressure) and urethral pressure profile studies (ie, urethral closure pressure profile), any technique
51736	XXX	Simple uroflowmetry (eg, stop-watch flow rate, mechanical uroflowmetry)
51741	XXX	Complex uroflowmetry (eg, calibrated electronic equipment)
51784	000	EMG studies of anal or urethral sphincter, other than needle, any technique
51785	000	Needle EMG studies of anal or urethral sphincter, any technique
51792	000	Stimulus evoked response (eg, measurement of bulbocavernosus reflex latency time)
51797	ZZZ	Voiding pressure studies, intra-abdominal (ie, rectal, gastric, intraperitoneal) (list separately in addition to code for primary procedure)

day, in a different location, and by a different provider than the professional interpretation; it is, therefore, critical that these variables be carefully documented not only in the billing records but in the medical record as well.

Uroflowmetry is a common diagnostic test that can be performed alone or in conjunction with some of the other codes within this family. Simple uroflowmetry requires observation of patients, offers limited information, requires limited documentation, and is rarely performed in the contemporary urologic practice. Complex uroflowmetry can be performed with limited staff involvement and, because it requires a full bladder, is often performed during routine nursing intake of patients as a standing order (for example, at the same time as collection of a urine specimen). Optimal documentation includes an indication based on medical necessity and an order for the test; this may be accomplished by indication-based protocol, but the medical record should clearly reflect the reason—for example, “uroflowmetry ordered today to assess response to a-blocker therapy after urinary retention.”

Cystometry (cystometrogram) in the contemporary urology practice is usually performed by calibrated electronic equipment, and in some cases the equipment also generates the documentation of the technical portion of the procedure(s). Machine-generated documentation should be imported into the medical record when possible and not stored separately from other records used to support coding and reimbursement. Documentation should include the indication for the procedure(s), the equipment and supplies used (for example, the size of the catheter), the method (for example, rate of bladder filling or type of electromyography [EMG] electrode used), and the raw observations of the person conducting the test (for example, “first urge to void”). If additional procedures are performed at the same setting, each component of the procedure should be documented clearly in order to support coding; for example, in order to support 51729, the document should indicate that cystometry, voiding pressure, and urethral pressure studies were conducted separately. A statement that a patient was able to void should be included, and studies that depend on patient voiding (for example 51729) cannot be supported if the patient was unable to void. The professional interpretation of the urodynamic testing requires a summative narrative, should address the observations made during the technical performance of the procedure, and should be separate and distinct from documentation of the actual procedure. If multiple procedures are performed, each component’s interpretation should be readily identifiable in the summation.

Coding best practice

As discussed previously, if the TC is performed on a different day, by a different provider, and/or in a

different location from the professional interpretation, it is necessary to split the services and append the appropriate modifiers (TC, 26) to each of the selected codes. “Incident to” rules of coding may apply if the technical portion of the procedure is performed by supervised personnel; care should be taken to bill under the supervising provider’s ID and follow other “incident to” rules. The date of service, not the ordering provider, determines the proper place of service and billing provider in those circumstances.

Note also that all codes with the exception of uroflowmetry codes have global periods of 000 assigned. As such, E&M codes reported on the same date as the -TC, -26, or global service (neither -TC or -26 appended) requires appropriate use of modifier -25.

Injection Procedures

Documentation

Injection or implantation of medication in the urology office is a common and minor procedure that lends itself well to template documentation (Table 9). Many electronic medical records have robust modules for medication administration, and these should be used whenever possible to take advantage of clinical decision support and structured data entry; these templates also drive best documentation practices. The medical record should contain a discrete indication and order for the medication procedure. The document should include exact injection site, laterality if pertinent, drug, dosage, NDC, lot number, expiration date, and absence or presence of complications. The administration procedure note should clearly explain whether the drug/biologic was acquired and provided by the physician office or by the patient (for example, a prescription or specialty pharmacy shipment).

Coding best practice

The injection/implantation procedure and medication are typically coded separately with CPT codes and appropriate HCPCS (J) codes. Injections are often provided by staff under “incident to” guidelines and this is allowed without physician contact for the injection visit as long as the injection is part of the treatment plan developed and periodically reviewed by a qualified provider; this underscores the importance of documenting a physician order. Note the specificity of the injection codes and that antineoplastic medications are coded with 96402 despite the subcutaneous or intramuscular route. Medications often have different J codes for different dosage forms and it is sometimes necessary to append “units” to the J code in order to receive proper reimbursement. Reporting of the

Table 9
Injection procedures

Code	Global	Description
11980	000	Subcutaneous hormone pellet implantation (implantation of estradiol and/or testosterone pellet)
11981	XXX	Insertion, nonbiodegradable drug delivery implant
11982	XXX	Removal, nonbiodegradable drug delivery implant
11983	XXX	Removal with reinsertion, nonbiodegradable drug delivery implant
54200	010	Injection procedure for Peyronie disease
54235	000	Injection of corpora cavernosa with pharmacologic agent(s) (eg, papaverine, phentolamine)
96372	XXX	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
96402	XXX	Chemotherapy administration, subcutaneous or intramuscular; hormonal antineoplastic
J0270	XXX	Injection, alprostadil, 1.25 mg
J0900	XXX	Injection, testosterone enanthate and estradiol valerate, up to 1 mL
J1060	XXX	Injection, testosterone cypionate and estradiol cypionate, up to 1 mL
J1070	XXX	Injection, testosterone cypionate, up to 100 mg
J1080	XXX	Injection, testosterone cypionate, 1 mL, 200 mg
J2440	XXX	Injection, papaverine hydrochloride, up to 60 mg
J2760	XXX	Injection, phentolamine mesylate, up to 5 mg
J3120	XXX	Injection, testosterone enanthate, up to 100 mg
J3130	XXX	Injection, testosterone enanthate, up to 200 mg
J3140	XXX	Injection, testosterone suspension, up to 50 mg
J3150	XXX	Injection, testosterone propionate, up to 100 mg
S0189	XXX	Testosterone pellet, 75 mg
J9219	XXX	Leuprolide acetate implant, 65 mg
J3315	XXX	Injection, triptorelin pamoate, 3.75 mg
J9202	XXX	Goserelin acetate implant, per 3.6 mg
J9217	XXX	Leuprolide acetate (for depot suspension), 7.5 mg

amount of drug is allowed up to full amount in the vial.

Most of the codes in this family are assigned a global period of XXX; however, current CCI bundling edits include E&M codes so E&M services provided on the same date of service require the use of modifier -25 and the appropriate documentation to support use of the modifier. Billing of E&M codes in conjunction with injection codes are a historical target of payer audits and must be medically necessary.

Intracorporal injection of vasoactive medications deserves separate mention for several reasons. First, the CPT code 54235 has a 000 global period and E&M services thus require appropriate modifiers. Second, the procedure typically administering 2 or 3 medications in different dosages; as such, careful attention to proper J codes and units is recommended. The most common medications and their codes are J2440

papaverine, J2760 phentolamine, and J0270 alprostadil—a combination often referred to as Trimix by compounding pharmacies. Finally, because Medicare considers this a procedure to train a patient for self-injection and typically allows billing 54235 once in a patient's lifetime, it is important to ensure the patient has not received a previous injection (and to so document).

Transurethral Microwave Thermotherapy (TUMT) and Transurethral Needle Ablation (TUNA) of Prostate

Documentation

Ablative treatments for BPH performed in the office are invasive procedures, involve expensive disposable items, and require careful and thorough documentation (Table 10). Special considerations include the importance of documenting the treatment setting, the equipment used,

Table 10 Transurethral microwave thermotherapy and transurethral needle ablation of prostate		
Code	Global	Description
53850	090	Transurethral destruction of prostate tissue; by microwave thermotherapy
53852	090	Transurethral destruction of prostate tissue; by radiofrequency thermotherapy

the energy settings and times of treatments, and the monitoring and supervision involved. The treatment equipment often provides a log of energy and times, and this should be made a part of the permanent medical record.

Coding best practice

Note that these procedures include a global period of 90 days (including the first preoperative day) and, as such, require that additional services be appended with appropriate modifiers. Supplies used during the procedure, including the treatment catheters, bladder catheters, and other disposables, are considered included and generally not reimbursed separately.

Pelvic Floor Therapy (PFE) and Biofeedback

Documentation

Many payers require that patients fail other therapy (timed voiding or pelvic floor exercises at home, for example) prior to reimbursing for biofeedback and physical therapy, so it is important to document previous unsuccessful therapies and the indications for the procedure (Table 11). Many payers require that a clear plan of treatment, including measurable goals, be included in the patient record. Each treatment session should include documentation of the session number, time spent during treatment, equipment used, and findings, including interim assessments of progress toward goals.

Coding best practice

These procedures are often provided by staff under “incident to” guidelines and this is allowed without physician contact for the injection visit as long as the therapy is part of the treatment plan developed and periodically reviewed by a qualified provider. Medicare may require use of quality reporting CPT II codes for pelvic floor exercise treatment series. Space does not permit full discussion of proper use of G codes; the authors recommend that readers review current Medicare

Table 11 Pelvic floor therapy and biofeedback		
Code	Global	Description
90911	XXX	Biofeedback training, perineal muscles, anorectal or urethral sphincter, including EMG and/or manometry
97032	XXX	Application of a modality to 1 or more areas; electrical stimulation (manual), each 15 min
G0283	XXX	Electrical stimulation (unattended), to 1 or more areas for indication(s) other than wound care, as part of a therapy plan of care
G8990	XXX	Other physical or occupational primary functional limitation, current status, at therapy episode outset and at reporting intervals
G8991	XXX	Other physical or occupational primary functional limitation, projected goal status, at therapy episode outset, at reporting intervals, and at discharge or to end reporting
G8992	XXX	Other physical or occupational primary functional limitation, discharge status, at discharge from therapy or to end reporting

guidelines for quality reporting methods required for payment. EMG diagnostic services may be used in conjunction with biofeedback or pelvic floor exercise but can only be reported if performed to determine baseline readings or to record measurement of progress. Finally, many payers, including Medicare, have benefit caps related to total amount that are paid for physical therapy services, underscoring the importance of predetermination of benefits for patients.

SUMMARY

Adherence to some general principles of documentation and coding serves as a firm foundation for urologists committed to compliant billing of most office procedures. Complex and new procedures can be coded correctly with the assistance of readily available subject matter experts and other resources. Maintaining current competency in this rapidly changing field is imperative to

optimize reimbursement, meet regulatory requirements, and minimize risk.

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Office-Based Behavioral Therapy for Management of Incontinence and Other Pelvic Disorders

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KEYWORDS

- Lower urinary tract symptoms • Behavioral treatment • Lifestyle modification • Timed voiding
- Pelvic floor muscle training • Bladder training

KEY POINTS

- Behavioral treatment with pelvic floor muscle training is the first-line treatment option for patients with lower urinary tract symptoms.
- Urology lends itself to a multidisciplinary model of a Bladder and Pelvic Floor Disorder service that provides comprehensive surgical and medical care.
- Before prescribing a behavioral intervention, assessment of the pelvic floor musculature is performed to evaluate strength, tone, and ability to contract.
- Certain lifestyle practices can cause lower urinary tract symptoms, and changes in these practices arising from evidence-based research can have a positive effect in decreasing symptoms.
- Bladder training is an education program that teaches the patient to restore normal bladder function by gradually increasing the intervals between voiding.
- Pelvic floor muscle training has been shown to decrease urgency, stress, and mixed incontinence in women, and should be offered preoperatively to men undergoing radical prostatectomy surgery.
- The best outcomes with behavioral treatments are achieved when they are provided by a knowledgeable professional in a supervised program, making it an ideal and necessary service in urology.

INTRODUCTION

Behavioral treatment with pelvic floor muscle training (PFMT) is the first-line treatment option for persons with lower urinary tract symptoms (LUTS) including urinary incontinence (UI), overactive bladder (OAB), urgency, frequency, nocturia, incomplete bladder emptying, and pelvic floor muscle (PFM) spasm.¹ These interventions, categorically referred to as conservative management, improve symptoms through pelvic floor muscle

strengthening, identification of lifestyle habits, and frequently changing a person's behavior, environment, or activity that are contributing factors or triggers.² Such a program can be initiated after simple non-invasive urologic assessment in most patients, and should be considered the mainstay of urology care of men and women with incontinence and related voiding and pelvic floor disorders. The goals of conservative treatment are to correct voiding patterns, improve the ability to suppress urgency, and thereby to increase bladder

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capacity and to lessen the frequency and amount of both stress and urgency urinary incontinence. Interventions such as bladder training (BT) and PFM rehabilitation attempt to decrease incontinence and OAB symptoms, and aid bladder emptying through increasing awareness of the function and coordination of the PFMs, so as to gain muscle identification, control, and strength and to decrease bladder overactivity. These interventions involve learning new skills through extensive one-on-one patient instruction on techniques for preventing urine loss, urgency, and other symptomatology. These methods have a large body of evidence-based research,¹ and recommended as treatment for UI which supports this type of program in non-neurogenic OAB by multiple organizations^{3,4} and international guidelines.¹ The behavioral treatments discussed in this article are the ones commonly provided in urology practice for LUTS, and a behavioral treatment pathway is illustrated in **Fig. 1**. The different interventions are shown in **Fig. 2**, and **Box 1** lists the components.

BEHAVIORAL TREATMENT MODELS FOR LUTS

Urologic diseases encompass a wide scope of illnesses of the genitourinary tract of men and women, including conditions that are congenital and acquired, malignant and benign, medical and surgical. These diseases span all age groups and many conditions (eg, incontinence, voiding dysfunction, benign prostatic hyperplasia) are chronic in nature, and require care for the duration of a patient's life. With the growing shortage of urologists, the difficulty of recruiting them in some regions of the country,⁵ and the aging population, many practices are turning to advanced practice providers (APPs), nurse practitioners, or physician assistants to help fill the need to provide adequate and accessible care. An APP (sometimes referred to as a physician extender), when properly trained and deployed, enables practices to provide an increased number and higher quality of services, and allows the urologist to treat more patients in a timely manner. These highly trained "extenders" can assist the urologist by accepting delegated tasks of greater complexity than had previously been delegated to registered nurses and office assistants with less training.⁶

LUTS (both storage and emptying abnormalities) and pelvic floor dysfunction are areas of urologic practice that have seen tremendous growth in the use of APPs. These conditions have been inadequately treated and poorly addressed by the medical community and industry, despite substantial impact on health, self-esteem, and quality of life. APPs providing behavioral treatments

(sometimes referred to as continence nurse practitioners) have emerged in urology practices, specifically to assess and provide nonsurgical treatment of LUTS such as UI, OAB, urgency, frequency, urinary retention, pelvic pain, and interstitial cystitis (**Box 2**). Urology lends itself to a multidisciplinary model of a Bladder and Pelvic Floor Disorder service that provides comprehensive surgical and medical care. These centers are an attractive addition to a hospital or urology practice because they provide secure revenue-generating services, and there are increasing opportunities for billing of APP services. A Bladder and Pelvic Floor Disorder center usually offers the combined knowledge of a multidisciplinary group of experts in UI, voiding, and pelvic floor dysfunction. Changes in reimbursement for nonsurgical treatments such as biofeedback therapy, pelvic muscle electrical stimulation (E-stim), and posterior tibial nerve stimulation have allowed urologists to consider the expansion of current treatments (pharmacologic and surgical) to include alternative treatments such as PFM rehabilitation.

ASSESSMENT BEFORE BEHAVIORAL TREATMENTS

Before initiating nonsurgical treatment a focused and detailed history is essential. History is one of the most important steps in evaluating the patient with LUTS, as findings will direct behavioral treatment. Symptoms include urgency, frequency, and nocturia, stress and urgency-related incontinence, postvoid dribbling, nocturnal enuresis, straining to void, hesitancy, weak stream, and incomplete bladder emptying and retention. Understanding the onset, duration, characteristics, and progression of the LUTS is important. Many patients will report situational antecedents or "triggers."⁷

Appropriate treatment with PFMT should always include an assessment of PFM contraction and relaxation, because the effect of PFMT depends on whether the contractions and relaxations are performed correctly. Digital (eg, vaginal or rectal) PFM assessment is a form of biofeedback performed before starting behavioral therapy. PFM strength can be determined in women by inserting 1 or 2 fingers into the vagina to the level of the first knuckle. Muscular attachments along the pubic arch and the insertion of the levator ani and coccygeus muscles are palpated.⁸ The levator ani can be palpated just superior to the hymeneal ring, at the 4- and 8-o'clock positions, to determine strength and whether palpation reproduces any discomfort or tenderness. The patient is asked to contract the PFMs around the examiner's finger with as much force and for as long as able. The

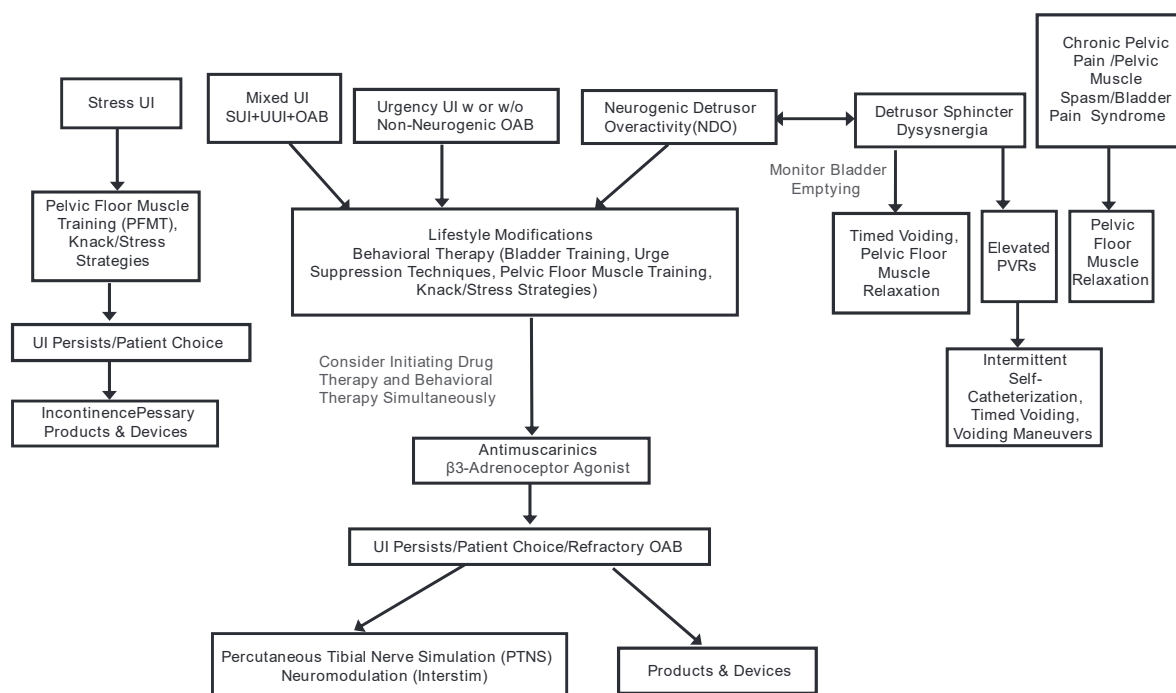


Fig. 1. Behavioral treatment care pathway for lower urinary tract symptoms. OAB, overactive bladder; PVR, postvoid residual volume; SUI stress urinary incontinence; UI, urinary incontinence; UUI, urge urinary incontinence.

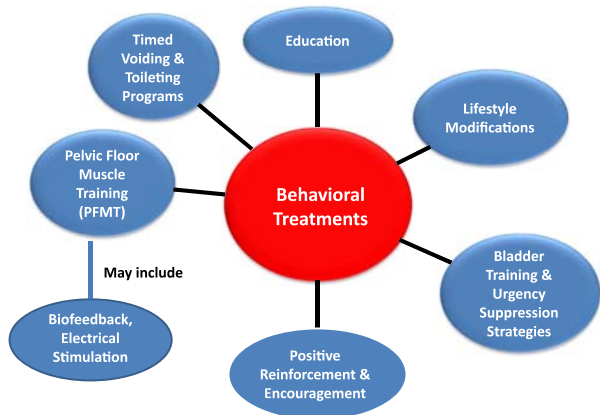


Fig. 2. Components of behavioral treatment.

patient is asked to squeeze or pull in and upward with vaginal muscles in short, fast contractions called “flicks.” It is important to realize that when asked to contract the pelvic muscle, women will often use the wrong muscle, strain down, and perform a Valsalva maneuver, or fail to activate all layers of the pelvic musculature. The examiner notes through observation whether accessory muscles (such as gluteal and abdominal muscles) also contract. When assessing PFM strength, 3 criteria should be used⁹ and the results noted:

- Pressure: the amount of pressure or strength of the muscle contraction, which can range from imperceptible to a firm squeeze
- Duration: the number of seconds that the examiner feels the muscle contraction
- Alteration in position: in a well-supported PFM, the muscle contraction can lift the base of the examiner’s finger. Note use of

accessory muscles (abdominal movement, gluteal lifting). If the patient has a pelvic muscle spasm (inability to relax muscle), note the degree

Assessment of the PFMs in men and women can also be performed by evaluating the contraction and tone of the anal sphincter, and PFM exercises can be taught during the rectal examination. Have the patient relax and bear down. As the sphincter relaxes, gently insert the index finger into the anal canal in a direction pointing toward the umbilicus. Note if the resting sphincter tone is weak, moderate, or strong. Normally, the muscles of the anal sphincter close snugly around the entire circumference of the examiner’s finger. In the rectum, the distal external sphincter is felt just inside the anal canal. The puborectalis portion of the levator ani muscle can be palpated about 2.5 to 4 cm from the anal verge. To assess the

Box 1
List of behavioral interventions

- Education on lower urinary tract function, normal voiding, and healthy bladder habits
- Behavior modification/coping skills to maximize bladder control
- Monitoring symptoms and outcomes through the use of bladder diaries and patient questionnaires
- Lifestyle modifications
- Bladder training with urgency suppression
- Pelvic floor muscle rehabilitation to include biofeedback therapy
- Ensure long-term transference of skills learned to the patient’s daily life
- Stimulation in refractory patients to include pelvic floor electrical stimulation to increase strength, coordination, and control of bladder and pelvic muscles, and posterior tibial nerve stimulation to decrease urgency and frequency

Box 2
Bladder and pelvic floor disorder center: specific APP interventions

- Comprehensive evaluation of symptoms and associated disorders
- Analysis of bladder diaries (pre-, during, and posttreatment) and standardized questionnaires
- Instructions on voiding maneuvers (postvoid micturition, improvement in bladder-emptying techniques)
- Pelvic floor muscle assessment using a validated scale (pelvic examination, levator ani palpation, anal sphincter muscle assessment)
- Bladder training and urge-suppression treatments
- Pelvic floor muscle training with the addition of biofeedback and/or pelvic floor muscle electrical stimulation
- Pelvic floor muscle “down-training” for pelvic pain and muscle spasm
- Medication prescribing
- Neuromodulation treatment that includes:
 - Programming and management of Interstim
 - Delivery of posterior tibial nerve stimulation treatments
- Pessary fitting and maintenance
- Catheter management (indwelling catheter [urethral and suprapubic] changes and management, postoperative suprapubic catheter changes, intermittent catheterization teaching and long-term management, urethral stricture catheterization teaching)
- Evaluation, fitting, and education on use of external devices (male external catheter, external pouches, toileting-assistive products)
- Counseling on absorbent containment products

strength of the sphincter muscle, ask the patient to tighten the rectum. The examiner should feel a grip, pulling in around entire finger circumference.

Patients are asked to complete a self-monitoring 3-day bladder diary on a daily basis; this is a simple and practical method of obtaining information on voiding behavior.¹⁰ The diary should be constructed in such a way that it provides information regarding sensation of urgency, urine leakage episodes, and the events surrounding these episodes. Before and during treatment, the diary is reviewed to determine voiding patterns: during the day, during the night; frequency of urination; if urine leakage is associated with urgency, or following the ingestion of a bladder irritant such as caffeinated beverages.

Symptoms will direct the interventions. Many providers are interested in the patient noting the type and quantity of absorbent incontinence pads used, and quantifying the amount of urine leakage. An example of a Frequency Volume Bladder Diary is shown in **Fig. 3**. Bladder diaries are also the best noninvasive tools available to objectively monitor the effect of treatment. Keeping a diary is thought to empower patients and make them more aware of their drinking and voiding habits, thus helping them to retrain the bladder more effectively.¹¹

BEHAVIORAL TREATMENTS

Education is the initial component of behavioral treatments as patients are taught about the function of the lower urinary tract, the mechanics of bladder storage and emptying, the importance of the urinary sphincter and PFM, and healthy bladder habits.¹² Types of behavior used by women to empty their bladders may be related to the development and worsening of LUTS.¹³ These behaviors include:

1. Antecedents: attending to the urge to void, accessing the toilet to empty the bladder, adopting a proper position
2. Micturition: emptying urine into toilet or toilet receptacle, straining
3. Consequences: incomplete bladder emptying, incontinence, bladder control

For example, some women ignore the urge to void and do not urinate while they are at work, delay voiding because of limited work breaks,^{14,15} or have a decreased opportunity to leave their work stations to void.¹⁶ As a result, women may develop a habit of voiding at any time (regardless of the presence of the sensation to void), strain or bear down to void quickly, or void on an

NAME: _____ DATE: _____

INSTRUCTIONS:

☐ Column 1: write in the time you void, have an "Accident" or drink a beverage

☐ Column 2: Next to the time, record if you voided and the amount (in ounces or mL)

☐ Column 3: Mark every time you have an incontinent episode or urine leakage and circle if Large or Small amount.

☐ Column 4: Write the urine leakage, such as urinary urgency, sneezing, lifting, coughing, laughing, bending, pain, couldn't make it to the bathroom, and so on.

☐ Column 5: Write the type of fluid you drank (for example: coffee, water, orange juice, beer) and estimate the amount (for example: one 8-oz cup of coffee).

COLUMN 1	COLUMN 2	COLUMN 3		COLUMN 4	COLUMN 5
TIME	AMOUNT URINATED IN TOILET (OUNCES OR MILLILITERS)	LEAKAGE OF URINE (INCONTINENT EPISODE) AT ANY TIME		REASON FOR URINE LEAKAGE (URGENCY, COUGHING, BENDING)	AMOUNT AND TYPE OF FLUID INTAKE
		Large	Small		
		Large	Small		
		Large	Small		
		Large	Small		
		Large	Small		
		Large	Small		
		Large	Small		
		Large	Small		
		Large	Small		
		Large	Small		
		Large	Small		
		Large	Small		
		Large	Small		
		Large	Small		
		Large	Small		
		Large	Small		

Circle the product you are using

Write the number of products used: _____

Pantliners

Pads

Protective Underwear

Briefs or "diapers"

Comments: _____

Fig. 3. Frequency volume bladder diary.

infrequent basis. Too frequent voiding makes the bladder more sensitive to a smaller amount of urine within¹⁷ and may, over time, decrease bladder capacity. Overdistension of bladder may occur as a result of infrequent voiding. Behavioral interventions address optimal voiding behavior, posture, and position, to ensure complete bladder emptying (**Patient Guide 1**).

LIFESTYLE MODIFICATIONS

In many instances, lifestyle practices can contribute or cause LUTS, bladder and/or pelvic pain. Many lifestyle habits are modifiable and these modifications are part of behavioral treatment. Evidence-based research (**Table 1**) has shown that lifestyle changes can decrease LUTS. The following are key elements of a lifestyle modification program:

- Maintaining adequate fluid intake
- Modifying the diet to eliminate possible bladder irritants
- Regulating bowel function to avoid constipation and straining during defecation
- Smoking cessation
- Weight reduction

Altering Fluid Intake and Managing Volume

Individuals may practice either restrictive or excessive fluid intake. Working women often report limitations of fluid intake and avoidance of caffeinated beverages as strategies to avoid urinary symptoms.¹⁴ However, adequate fluid intake may be needed to eliminate irritants from the bladder. Underhydration may play a role in the development of urinary tract infections and may decrease the

Patient Guide 1**Lifestyle changes that can improve bladder symptoms****Maintain Healthy Bladder Habits**

Here are some tips on good toileting techniques:

- Empty your bladder in a relaxed and private place. Worry and tension can make bladder emptying more difficult.
- You should sit on the toilet seat and not “hover” over the toilet, as sitting relaxes your pelvic floor muscles so you can completely empty your bladder.
- Sit with your feet flat on the floor. If your feet dangle, place a book under your feet for support.
- Breathe gently as you urinate. If possible, minimize bearing down or straining to start your urine stream.
- *Relax your pelvic floor muscles* to start your urine stream.
- *Do not* strain or push down on your bladder with your hands or stomach to help urinate.
- Keep your stomach and pelvic floor muscles relaxed while the bladder empties completely.
- Make sure your bladder feels completely empty before getting off the toilet.

Moderate your liquid and beverage intake

Many people who have bladder problems will drink less, hoping they will need to urinate less often. Although drinking less liquid does result in less urine in your bladder, a much smaller amount of urine may be more highly concentrated and irritate the lining of your bladder. Concentrated urine (dark yellow, strong smelling) may cause you to go to the bathroom more frequently. Also, drinking too little fluids can cause dehydration. Do not limit your fluids to control your bladder symptoms unless your doctor or nurse tells you to.

Other people may increase the amount they drink because they think more urine in the bladder will cause less bladder pain and discomfort. But drinking too much fluid will cause you to go to the bathroom more often. You should avoid extremes in the amount you drink (neither too much nor too little).

Normal fluid intake is 50 to 70 oz (1 oz = 30 mL) of liquid each day. This means that each day, you should consume the equivalent of 6 to 8 8-oz glasses of liquids (any beverages and soups), much of which can be in the form of solid foods. This should produce a healthy 40 to 50 oz of urine in 24 hours. People who work in hot climates or exercise heavily need more fluids because of loss through perspiration, but their urine output should still be approximately 40 to 50 oz. Do not drink large amounts at one time; instead, sip 2 to 3 oz every 20 to 30 minutes between meals. It is very unlikely that you will need to drink more than 2 quarts (or 8 cups) of total fluids each day.

Monitor your diet and medications

Certain food and beverages can irritate the bladder and make symptoms worse. These include alcoholic beverages, caffeinated foods and/or carbonated beverages (soft drinks, coffee or tea, chocolate, energy drinks), tomato-based products, citrus fruits and juices, spicy foods, and artificial sweeteners (eg, Equal). Also some over-the-counter drugs and prescription medications can worsen bladder problems (eg, Excedrin, Midol, Anacin). Do not stop taking prescription drugs without first talking to your health care provider. Keep a record of what you eat and drink and correlate this with lessening or worsening of your symptoms. Here is the caffeine content of some foods and drugs.

	Size	Caffeine Content (mg)
Coffee	8 oz	133 (range 102–200)
Tea	8 oz	53 (range 40–120)
Soft drinks	12 oz	35–72
Energy drinks	8–20 oz	48–300
Chocolate candies	Varies	9–33
Excedrin (extra-strength)	2 tablets	130
Anacin (maximum strength)	2 tablets	64
Vivarin, NoDoz	1 tablet	200

Maintain bowel regularity

Keeping healthy bowel habits may lessen bladder symptoms. Some suggestions include: (1) increase fiber-rich foods in your diet such as beans, pasta, oatmeal, bran cereal, whole wheat bread, fresh fruits and vegetables; (2) exercise to maintain regular bowel movements; (3) drink plenty of nonirritating fluids (water); (4) see your doctor if you have bowel problems.

Maintain a healthy weight

Being overweight can put pressure on your bladder, which may cause leakage of urine when you laugh or cough. If you are overweight, weight loss can reduce pressure on your bladder.

Stop smoking

Cigarette smoking is irritating to the bladder muscle. It can also lead to coughing spasms that can cause urinary leakage.

functional capacity of the bladder. Surveys of community-residing elders with LUTS report self-care practices to include the self-imposed fluid restriction, as they fear UI, urinary urgency, and urinary frequency.^{18–20} Excessive fluid intake can also be a problem, as intake of large volumes can trigger incontinence and OAB symptoms of urgency and frequency.²¹ Fluid intake averaging greater than 3700 mL/d has been associated with a higher voiding frequency and incidence of UI when compared with an intake of approximately 2400 mL/d.¹ Hashim and Abrams²² recommend

Table 1 Levels of evidence and recommendations for lifestyle modifications		
Lifestyle Practice	Levels of Evidence	Recommendations
Fluid	Fluid intake may play a minor role in the pathogenesis of UI	Minor decrease of fluid intake by 25% may be recommended provided baseline consumption is not less than 30 mL/kg a day <i>Grade of Recommendation: B</i>
Caffeine	Caffeine consumption may play a role in exacerbating UI. Small clinical trials do suggest that decreasing caffeine intake improves continence <i>Level of Evidence: 2</i>	Caffeine reduction may help in improving incontinence symptoms <i>Grade of Recommendation: B</i>
Bowel function	There is some evidence to suggest that chronic straining may be a risk factor for the development of UI <i>Level of Evidence: 3</i>	Further research is needed to define the role of straining during defecation in the pathogenesis of UI
Obesity	Massive weight loss (15–20 body mass index points) significantly decreases UI in morbidly obese women <i>Level of Evidence: 2</i> Moderate weight loss may be effective in decreasing UI especially if combined with exercise <i>Level of Evidence: 1</i>	Weight loss in obese and morbidly should be considered a first-line treatment to reduce UI prevalence <i>Grade of Recommendation: A</i>
Smoking		Further prospective studies are needed to determine whether smoking cessation prevents the onset, or promotes the resolution, of UI

Adapted from Moore K, Bradley C, Burgio B, et al. Adult conservative treatment. In: Abrams P, Cardozo L, Khoury S, et al, editors. Incontinence: Proceedings from the 5th International Consultation on Incontinence. Plymouth (United Kingdom): Health Publications; 2013. p. 1101–228; with permission.

decreasing fluid intake by 25% to reduce frequency, urgency, and nocturia, provided baseline consumption is not less than 1 L a day, and that increasing fluid intake by 25% and 50% can result in a worsening of daytime frequency.

Fluid intake should be regulated to 6- to 8-oz (177–236 mL) glasses or 30 mL/kg body weight per day, with a 1500 mL/d minimum at designated times unless contraindicated by a medical condition.

In older adults, there appears to be a strong relationship between evening fluid intake, nocturia, and nocturnal voided volume. Aging causes an increase in nocturia, defined as the number of voids recorded from the time the individual goes to bed with the intention of going to sleep, to the time the individual wakes with the intention of rising. To decrease nocturia precipitated by drinking fluids primarily in the evening or with dinner, the patient is instructed to reduce fluid intake after 6 PM and shift intake toward the morning and afternoon.²³ Wagg and colleagues²⁴ recommend that late-afternoon administration of a diuretic may reduce nocturia in persons with lower extremity venous insufficiency or congestive heart failure unresponsive to other interventions.

Influence of Dietary Bladder Irritants

Common dietary staples can cause diuresis or bladder irritability, contributing to LUTS. Up to 90% of patients with IC/BPS report sensitivities to a wide variety of comestibles.^{25–27} Caffeine intake has been associated with LUTS in both men²⁸ and women.²⁹ Caffeine is thought to affect urinary symptoms by causing a significant increase in detrusor pressure and an excitatory effect on detrusor contraction. Daily administration of oral caffeine (150 mg/kg) results in detrusor overactivity and increased sensory signaling in the mouse bladder.³⁰ The consumption of caffeinated beverages, foods, and medications should not be underestimated. In the United States, more than 80% of the adult population consumes caffeine in the form of coffee, tea, soft drinks, and energy drinks on a daily basis. The Boston Area Community Health³¹ reported on beverage intake and LUTS in a large cohort (N = 4144). Women who increased coffee intake by at least 2 servings per day had 64% higher odds of progression of urgency (P = .003). Women who had recently increased soda intake, particularly caffeinated diet soda, had higher symptom scores, urgency, and LUTS progression. Greater coffee or total caffeine intake at baseline increased the odds of LUTS (storage symptoms) progression in men (coffee: >2 cups/d vs none, odds ratio [OR] = 2.09, 95% confidence

interval [CI] 1.29–3.40, P-trend = .01; caffeine: P-trend < .001). Citrus juice intake was associated with 50% lower odds of LUTS progression in men (P = .02). Lohsiriwat and colleagues³² found that caffeine at a dose of 4.5 mg/kg caused diuresis and decreased the threshold of bladder sensation at filling phase, with an increase in flow rate and voided volume. Other findings suggest that high but not stable caffeine intake is associated with a modest increase in the incidence of frequent urgency incontinence.³³ It has been postulated that one-fourth of the cases of urgency and frequency with the highest caffeine consumption would be eliminated if high caffeine intake were eliminated.³⁴ Confirmation of these findings in other studies is needed before recommendations can be made.

In addition to caffeine, alcohol is also believed to have a diuretic effect that can lead to increased frequency. A survey conducted by the Interstitial Cystitis Network³⁵ found that 94% of 535 patients who responded reported that their bladder symptoms worsened when drinking various alcoholic beverages. Anecdotal evidence suggests that eliminating dietary factors such as artificial sweeteners (aspartame) and certain foods (eg, highly spiced foods, citrus juices, and tomato-based products) may contribute to LUTS, especially urgency and frequency. Current questionnaire-based data suggest that citrus fruits, tomatoes, vitamin C, artificial sweeteners, coffee, tea, carbonated and alcoholic beverages, and spicy foods tend to exacerbate LUTS, whereas calcium glycerophosphate and sodium bicarbonate tend to improve IC/BPS symptoms.²⁷

Assessment of daily caffeine intake on all patients with LUTS and instructions on the correlation between symptoms and caffeine intake are integral to clinical practice. It is recommended that patients with incontinence and OAB avoid excessive caffeine intake (eg, no more than 200 mg/d or 2 cups). The patient is instructed on an elimination diet by identifying possible irritating products on a one-by-one basis to discern whether symptoms decrease or resolve.

Regulating Bowel Function

Chronic constipation (defined as having less than 3 stools per week) and straining during defecation can contribute to LUTS, specifically UI and OAB. Constipation is associated with impaired bladder emptying and worsening of irritative bladder symptoms.³⁶ The close proximity of the bladder and urethra to the rectum and their similar nerve innervations make it likely that there are reciprocal effects between them.³⁷ According to Kaplan and colleagues,³⁸ animal studies and clinical data

support bladder-bowel cross-sensitization, or cross-talk between the bowel and bladder. The Epidemiology of Lower Urinary Tract Symptoms (EpiLUTS) II³⁹ survey of men and women (N 5 2160) aged 40 years or older indicated that OAB is more likely to be reported if either gender had chronic constipation or fecal incontinence, compared with those without OAB. In a case-control study of women with LUTS (n 5 820) and matched controls (n 5 148), constipation and straining during defecation were significantly more common among the women with LUTS, including detrusor overactivity and urgency, than among the controls.⁴⁰ Jelovsek and colleagues⁴¹ reported a 36% overall rate of constipation in women with UI and advanced pelvic organ prolapse.

Lubowski and colleagues⁴² reported that denervation of the external anal sphincter and PFMs may occur in association with a history of excessive straining on defecation. Many believe that if these are lifetime habits, they may have a cumulative adverse effect on pelvic floor and bladder function. Patients with LUTS often report self-care practices to cope with LUTS by limiting fluid intake, a strategy that can exacerbate constipation. As combined behavioral and drug therapy is recommended for patients with nonneurogenic OAB,³ an antimuscarinic can compound the problem. Therefore, as part of the behavioral treatment, an initial approach is to question the patient about bowel habits and, if reported, to manage constipation and normalize defecation. Self-care practices that promote bowel regularity are an integral part of any treatment care plan. Suggestions to reduce constipation include the addition of fiber to the diet, increased fluid intake, regular exercise, external stimulation, and establishment of a routine defecation schedule. High fiber intake must be accompanied by sufficient fluid intake. Improved bowel function can also be achieved by determining a timetable for bowel evacuation so that the patient can take advantage of the urge to defecate.²³

Smoking and Chronic Obstructive Pulmonary Disease

Conditions exist under which increased intra-abdominal pressure may promote the development of UI and urinary urgency, particularly in women. These conditions include pulmonary diseases such as asthma, emphysema, and chronic coughing, such as seen in persons who smoke and/or have chronic obstructive pulmonary disease (COPD). Coughing causes increased intra-abdominal pressure, which directly increases pressure in the bladder. Usually the sphincter

muscle is able to contract tightly to avoid leakage of urine. However, it is thought that persons who cough repetitively cause downward pressure on the pelvic floor resulting in repeated stretch injury to the pudendal and pelvic nerves, and weakening of the ligaments of the PFMs that support the external sphincter, so that incontinence, specifically stress UI (SUI), can occur. Nicotine may contribute to detrusor contractions, and tobacco products may have antiestrogenic hormonal effects that may influence the production of collagen synthesis.

Hrisanfow and Häggglund⁴³ surveyed 391 women and 337 men (aged 50–75 years) with COPD to determine the prevalence, characteristics, and status of UI. A response rate of 66% was obtained, and most patients had been diagnosed with moderate COPD. The prevalence of UI in this group of men and women with COPD was 49.6% in women and 30.3% in men. Women and men with UI had a significantly higher body mass index (BMI; calculated as weight in kilograms divided by height in meters squared, ie, kg/m²) than those without UI, and the most common type of UI in women was SUI (52.4%) and in men, postmicturition dribbling (66.3%). A United States population-based cohort study of 2109 women aged 40 to 69 years, including racially and ethnically diverse participants, found an adjusted association between a change in continence status and COPD at baseline but not with other comorbidities.⁴⁴ There is a significantly increased risk of UI among nonpregnant female heavy smokers, both former and current, compared with women who have never smoked.⁴⁵ A cohort study of 523 American women found that smoking before pregnancy in comparison with not smoking gave the highest independent risk for UI postpartum in multivariable analyses (OR 5 2.9, 95% CI 1.4–3.9).⁴⁶

No data have been reported that examine whether smoking cessation in women resolves incontinence. However, in a behavioral treatment practice, women who smoke are educated on the relationship between smoking and UI, and strategies designed to discourage women from smoking are often suggested.

Obesity

Obesity is an independent and modifiable risk factor for LUTS in women. There is a large amount of data, including several systematic reviews, demonstrating positive association between a BMI of 25 or greater and SUI as a high risk factor for other urinary tract symptoms including urgency, frequency, OAB, and urge UI (UUI).^{47–49} There is

evidence that obesity increases intra-abdominal pressure and places strain and stress on the pelvic floor structures, leading to weakening of the PFM, nerves, and blood vessels,^{50,51} while co-existing metabolic syndrome predisposes to UUI. The resultant impact on vascular perfusion and neural innervation may be a contributing cause of OAB symptoms and incontinence.⁵² Moreover, increases in waist circumference are associated with new incidence or progression of current UI.⁵³ In practice, the authors often see women who have stopped exercising because of LUTS. Weight loss is an acceptable treatment option for morbidly obese women. There is ample evidence-based research to support recommendations of weight loss as part of lifestyle interventions in obese patients with and without diabetes.^{54–56}

BLADDER TRAINING AND URGENCY REDUCTION STRATEGIES

Men and women who suffer from LUTS will develop abnormal voiding patterns and will practice preemptive or defensive voiding to prevent incontinence or urgency. These patients can benefit from BT, an education program that teaches the patient to restore normal bladder function by gradually increasing the intervals between voiding.^{57,58} Mechanisms of action are not well understood, but it is thought that BT:

- Improves cortical inhibition over detrusor contractions
- Facilitates cortical ability over urethral closure during bladder filling
- Strengthens pelvic striated muscles
- Alters behaviors that affect continence (eg, frequent response to urgency)

The main outcomes for a BT program are to:

1. Improve bladder overactivity by controlling urgency and decreasing frequency
2. Increase bladder capacity
3. Reduce urgency incontinence episodes

Detailed components of a BT program are listed in **Box 3**, and **Patient Guide 2** provides information on BT and the control of urgency and frequency. **Table 2** outlines the evidence and recommendations for BT, PFMT, and E-stim.

PELVIC FLOOR MUSCLE TRAINING

The cornerstone of conservative behavioral therapy is PFMT and exercise, with or without biofeedback. The rationale for this is that mastering a voluntary contraction of the PFMs will help to increase

urethral pressure, inhibit detrusor contractions, and prevent leakage of urine (**Box 4**). Arnold Kegel introduced PFM exercises, or Kegel exercises, in the late 1940s by developing a comprehensive program of progressive contractions of the levator ani muscle under direct supervision, and incorporating biofeedback technology. Most female patients presenting to a Urology Pelvic Floor Disorders Service have been told to do Kegel exercises and many report that the exercises have not improved their LUTS. However, few have undergone intensive training on how to identify, isolate, and strengthen the PFMs, making this type of behavioral treatment an important component of a specialized urology service.

A Cochrane review of PFM exercise⁵⁹ found that these treatments were effective for both SUI and mixed UI, can reduce urgency in comparison with placebo or no treatment, although women with pure SUI may have better outcomes. However, Hay-Smith and colleagues⁶⁰ noted in an abridged Cochrane systematic review that the best approach to PFMT has not been well defined with evidence-based research. Evidence from the literature suggests that supervised PFMT is more effective.^{1,61} PFMT has no significant side effects; cure rates for PFMT range from 16% to 27% and improvement rates from 48% to 80.7%. Bø and Hilde⁶² reported that long-term adherence to PFMT varied between 10% and 70%. Recommendations for PFMT in women and men are shown in **Table 2**.

Not being able to identify the PFMs or to exercise them correctly is probably the most common reason for poor outcomes with this treatment modality. It is a skill that patients seldom master on their first try, but, with repeated training, it can be used successfully and provides significant improvement in reducing LUTS. Confirming that patients have identified and isolated the correct muscles is essential, and often overlooked. In the past, most patients were given a pamphlet or brief verbal instructions on how to do PFM exercises and were told to “lift the pelvic floor,” or to interrupt the urinary stream. Although this simple approach may be adequate for some patients, it does not ensure that they understand which muscles to use when they begin a structured exercise program at home. Patients should be cautioned not to perform these exercises during voiding and to not stop and start urine flow as a form of exercising. This exercise has good face-value validity for effectiveness because many patients initially report an inability to stop the urine flow when it begins. However, there is some controversy regarding this practice because it is nonphysiologic and can be harmful.

Box 3**Components of a bladder-training program**

- Normal voiding is approximately 5 to 7 times per day. The goal of a bladder-training program is to achieve a comfortable voiding schedule with the least amount of urinary symptoms
- Analyze the bladder diary to determine voiding frequency and presence of urgency
- Set the initial voiding interval using these guidelines:
 - If voiding occurs on average every 30 to 60 minutes, initial voiding interval would be 30 minutes
 - If voiding occurs on average at least every 1 hour or greater, initial voiding interval would be 1 hour
 - Voiding interval is increased by 15 to 30 minutes per week depending on tolerance of the schedule (such as fewer incontinent episodes than the previous week, minimal interruptions to the schedule, and the patient's feeling of control over urgency and confidence to expand the voiding interval)
 - If voiding is missed, the patient should void as soon as he/she remembers or if it is inconvenient, and then void at next scheduled time
 - Goal is for the patient to void "before" the urge sensation of bladder fullness
 - Voiding regimen is only followed while awake
- Education about normal bladder control and methods to control urgency (called urgency-suppression strategies) so that an expanded voiding interval can be adopted. Strategies include:
 - Distraction
 - Relaxation techniques such as slow, deep breathing to consciously relax the bladder to combat a stressful rush to the toilet
 - Pelvic floor muscle contraction, performing 5 or 6 rapid, deliberate, and intense pelvic floor muscle contractions of 2 to 3 seconds in duration
- Patient should not rush or run to the bathroom, as increased anxiety may trigger incontinence
- Use of reminders such as a kitchen timer or stopwatch can be beneficial to helping the patient keep on a schedule
- Self-monitoring of voiding behavior using bladder diaries to determine adherence to the schedule, enhance self-awareness, evaluate progress, and determine whether the voiding interval should be changed
- Supervising health care professional to monitor progress, suggest adjustments to the voiding interval, and provide positive reinforcement to men and women undergoing bladder training at least weekly during the training period

Data from Moore K, Bradley C, Burgio B, et al. Adult conservative treatment. In: Abrams P, Cardozo L, Khoury S, et al, editors. Incontinence: Proceedings from the 5th International Consultation on Incontinence. Plymouth (United Kingdom): Health Publications; 2013. p. 1166; and Newman DK, Wein AJ. Managing and treating urinary incontinence. 2nd edition. Baltimore (MD): Health Professions Press; 2009. p. 260–3.

PFMs have a higher resting tone than other skeletal muscles. Low muscle tone is the impaired ability to isolate and contract the PFM in the presence of weak and atrophic muscles. Low-tone PFM dysfunction can be seen in patients with pelvic floor denervation, and contributes to pelvic organ prolapse, UI, vaginal laxity, and fecal incontinence. High muscle tone refers to the clinical condition of hypertonic, spastic PFM with resultant impairment of muscle isolation, contraction, and relaxation.⁶³ A high resting baseline with high variability and occasional spasms may be seen in patients with chronic pelvic pain syndromes (eg, bladder pain syndrome), overactive

bladder, or IC, and be associated with LUTS, pelvic pain, and sexual dysfunction with dyspareunia.

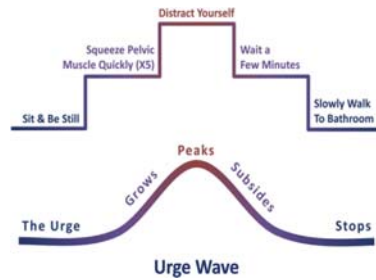
To respond to all physiologic needs, the PFM contains approximately 70% Type I or slow-twitch muscle fibers, and 30% Type II or fast-twitch muscle fibers.

- Type I fibers maintain static muscle tone, generate less intense, sustained contractions, and provide postural stability over time. Type I muscle fibers are also fatigue resistant.
- Type II fibers provide a mechanism for active, strong muscle contraction during increases

Patient Guide 2**Bladder training: controlling urgency and frequency**

Frequency is voiding often, usually 8 times or more in a 24-hour period. Frequency can worsen if you get into the habit of voiding “just in case,” which means that the bladder never fills completely and holds only a small amount of urine. It is better to wait until the bladder feels full.

Urgency is a sudden need to void immediately that can cause urine leakage on the way to the bathroom. Urgency follows a wave pattern; it starts, grows, peaks, and then subsides until it stops.



The key to controlling the urinary urge is *not* to respond by rushing to the bathroom. Rushing causes movement, which jiggles your bladder, which in turn increases the feeling of urge.

Controlling the Urge

The goal is for you to be voiding no more than every ____ hours. If you get the *urge* to void and it is not yet your scheduled voiding time, stop all activity and sit down if possible. Then try one or more of the following techniques that may help the urge to subside allowing the bladder to relax and give you more time to get to the bathroom:

- Take some slow, deep breaths through your mouth, concentrating on your breathing or
- Tighten your pelvic muscle *quickly and hard* several times in a row or
- Use mental distraction strategies such as concentrating on an activity, such as counting backwards from 100 by sevens, or reciting the words of a favorite song or nursery rhyme.

in intra-abdominal pressure by contributing to urethral closure, and build pelvic muscle strength. A decrease in the proportion of Type II fibers can occur with inactivity, nerve-innervation damage, and aging.

PFMT consists of repeated, high-intensity PFM contractions of both types of fibers (**Box 5**). Clinicians should provide specific instructions on location and isolation of the PFM, and the following instructions can be helpful:

- Without tensing the muscles of the legs, buttocks, or abdomen, imagine trying to control the passing of gas or pinching off a stool by tightening the ring of muscles around the anus. A closing and lifting sensation should be felt.
- (For men) Imagine moving the penis up and down without moving any other part of the body.

Patients should not overexercise the PFM, as women can develop levator ani myalgia by performing excessive exercises. Supervised PFMT has been shown to give better results than unsupervised exercises,¹ but the degree and type of supervision needed are uncertain. Age should not be a deterrent to PFMT.⁶⁴

Once patients demonstrate the ability to properly contract and relax the PFM, instructions for daily practice and exercise are provided (**Patient Guide 3**). The purpose of daily exercise is not only to increase muscle strength but also to enhance motor skills through practice. Specific exercise regimens vary considerably in frequency and intensity, and the ideal exercise regimen has not yet been determined. The authors recommend at least 45 to 60 pelvic muscle exercises per day, and use an “exercise prescription” as shown in **Box 6** to prescribe the home daily exercise program. Once patients are able to identify the muscle, they are instructed

Table 2
Grade of recommendation: PFMT, BT, E-stim

Treatment	Recommendations
PFMT postpartum	Postnatal women, immediately after delivery: Individually taught PFMT program that incorporates adherence strategies for women who had a vaginal delivery of a large baby (4000 g or more) or a forceps delivery <i>Grade of Recommendation: C</i> For postnatal women with persistent symptoms of UI 3 mo after delivery: PFMT is offered as first-line conservative therapy <i>Grade of Recommendation: A</i>
PFMT	Supervised PFMT should be offered as first-line conservative therapy to women with SUI, UUI, or MUI <i>Grade of Recommendation: A</i> The most intensive PFMT program possible should be provided (in terms of exercise dose, health professional [HP] teaching, and supervision) within service constraints; HP-taught and supervised programs are better than self-directed programs; more HP contact is better than less <i>Grade of Recommendation: A</i>
PFMT in women with SUI	PFMT is better than E-stim as first-line conservative therapy, particularly if PFMT is intensively supervised <i>Grade of Recommendation: B</i> PFMT is better than BT as first-line conservative therapy <i>Grade of Recommendation: B</i>
PFMT in men postprostatectomy	Some preoperative or immediate postoperative instruction in PFMT for men undergoing radical prostatectomy may be helpful <i>Grade of Recommendation: B</i> It is not clear whether PFMT taught by digital rectal examination offers any benefit over and above verbal or written instruction in PFMT <i>Grade of Recommendation: B</i> The use of BF to assist PFMT is currently a therapist/patient decision based on economics and preference <i>Grade of Recommendation: B</i>
PFMT 1 BT in women with UUI or MUI	PFMT and BT are effective first-line conservative therapy <i>Grade of Recommendation: B</i> For women with SUI or MUI, a combination of PFMT/BT may be better than BT alone in the short-term <i>Grade of Recommendation: C</i>
BT	BT is an appropriate first-line treatment for UI in women <i>Grade of Recommendation: A</i> Either BT or antimuscarinic drug may be effective, although BT may be preferred by some because it does not produce side effects and adverse events associated with drug therapy <i>Grade of Recommendation: B</i> There may be no benefit in adding brief written instruction in BT to drug therapy for incontinence, but it may improve episodes of frequency <i>Grade of Recommendation: B</i> A combination of PFMT/BT may be better than PFMT alone in the short term for women with symptoms of SUI or MUI <i>Grade of Recommendation: B</i> Clinicians and researchers should refer to the operant conditioning and educational literature to provide a rationale for their choice of training parameters or approach <i>Grade of Recommendation: D</i> Health Professionals should provide the most intensive BT supervision that is possible within service constraints. <i>Grade of Recommendation: D</i>

(continued on next page)

Table 2
(continued)

Treatment	Recommendations
E-stim	E-stim plus PFMT or BF-assisted PFMT program does not appear to add benefit <i>Grade of Recommendation: B</i> For men with postprostatectomy incontinence, there does not appear to be any benefit of adding E-stim to a PFMT program <i>Grade of Recommendation: B</i>

Abbreviations: BT, bladder training; E-stim, pelvic floor electrical stimulation; MUI, mixed urinary incontinence; PFMT, pelvic floor muscle training; SUI, stress urinary incontinence; UUI, urge urinary incontinence.

Adapted from Moore K, Bradley C, Burgio B, et al. Adult conservative treatment. In: Abrams P, Cardozo L, Khoury S, et al, editors. Incontinence: Proceedings from the 5th International Consultation on Incontinence. Plymouth (United Kingdom): Health Publications. 2013; p. 1101–228; with permission.

to perform a series of “quick flicks” or 2-second contractions followed by sustained (endurance contractions) contractions of 5 seconds and longer. It is equally important to relax the muscle completely between each muscle contraction. Patients are encouraged to aim for a high level of concentrated effort with each PFM contraction, as greater contraction intensity is associated with improvement in PFM strength.

A common error in contracting the PFMs is to simultaneously contract the abdominal, gluteal, or adductor muscles, which may mask the strength of the PFM contraction. Abdominal contraction increases intra-abdominal pressure that mechanically elevates bladder pressure, so it is important to measure and prevent concurrent use of abdominal contraction.

To avoid muscle fatigue, it is usually recommended that patients space the exercises across 2 sessions per day. Exercising in the supine position is often recommended at first, because it is the least challenging and facilitates concentration during the learning phase. However, it is important for patients to progress to the more difficult positions (eg, sitting, standing) with time, to become comfortable and skilled in using the muscles and to

prevent incontinence in the positions assumed in daily life. Self-monitoring practice through the use of a calendar record and audio taped material that reviews the exercises can improve protocol compliance. Improvement in symptoms may not occur for 2 to 4 months, so patient expectations are important for adherence to these interventions.

In addition to planned exercises, contracting the muscle prior to the event that triggers urine leakage is also taught. This preventive PFM contraction is referred to as the “knack” or stress strategy.^{65,66} This technique is an acquired motor skill that requires the patient to anticipate the urine leakage. Contracting the PFMs immediately before a sneeze or cough, or when lifting or changing position can close the sphincter, preventing urine leakage.

Rehabilitating the PFMs can be central in resolving pelvic pain when muscle spasm is present. Using PFMT in patients with high-tone PFM to enhance muscle relaxation is referred to as down-training. Teaching a muscle to relax is often more difficult than teaching it how to contract (up-training). Patients with pain will often benefit from biofeedback-assisted PFMT. The patient can correlate PFM movement with the biofeedback visual signal. Once they are able to feel the muscle release and relax, patients can begin coordination of relaxation following a contraction.

Box 4 **Pelvic floor muscle exercise mechanisms of action**

1. Urethral closure through increases in urethral pressure
2. Mechanical pressure increase that causes lifting of the endopelvic fascia, which presses the urethra upward toward the pubic symphysis
3. Pelvic muscle “reflex” contraction that precedes increased bladder pressure and may inhibit bladder overactivity

PFMT PREPROSTATECTOMY AND POSTPROSTATECTOMY

UI is a common complication of radical prostatectomy (RP), regardless of the technique used.⁶⁷ Continence rate is reported to be 10% to 41% after open RP and between 13.1% and 68.9% after robot-assisted RP.⁶⁸ Urology practices have begun to include various levels of PFMT for men undergoing RP; however, translation from research to practice has not been optimum because most men undergoing radical prostatectomy do

Box 5**Teaching pelvic floor muscle exercises**

1. Before exercising, patient should urinate so the bladder is empty. Significant stresses are placed on the pelvic floor muscles as the patient attempts to follow through on the demanding exercise schedule. These weak muscles will rapidly fatigue with all the exercising, and if they must also support a full bladder in addition to being exercised, they then will not receive maximum benefit from the strengthening program.
 - A successful method is to have the patient imagine trying to control the passing of gas or pinching off a stool, or imagine being in an elevator and feeling the urge to pass gas. In these situations, a person will automatically tighten or pull in the ring of muscle around the rectum, which is the posterior pelvic muscle.
2. One exercise consists of both "tightening and relaxing." Patient should be instructed to relax between each muscle tightening.
3. Exercise in 3 positions:
 - Sitting upright in a firm seat and straight-backed chair, knees slightly apart, feet flat on the floor or legs stretched out in front and crossed at the ankles
 - Standing by a chair, knees slightly bent with feet a shoulder-width apart and toes slightly pointed outward. Can also exercise standing and leaning on a counter top
 - Lying down flat or with head slightly elevated, knees bent and feet slightly apart
4. Have patient monitor for accessory muscle (eg, thigh and gluteal) contraction. Often patients will hold their breath; to prevent this, have the patient count out loud.
5. Have patients identify situations that cause urine leakage (eg, coughing, sneezing on way to bathroom) and teach them to purposefully contract the pelvic floor muscles when such a situation is imminent.

Adapted from Newman DK, Wein AJ. Managing and treating urinary incontinence. 2nd edition. Baltimore (MD): Health Professions Press; 2009. p. 271–5; with permission.

not receive PFMT. Evidence-based results demonstrate that early biofeedback-assisted PFMT not only hastens the recovery of urinary continence after radical RP but allows for significant improvements in the severity of incontinence, voiding symptoms, and PFMs 12 months postoperatively. **Table 3** reviews some of the recent research in this area of PFMT.

Biofeedback-assisted PFM exercise is a method by which the patient is immediately made aware of the physiologic state of the PFM. This adjunctive technique may be especially helpful in patients who are having difficulty identifying and isolating the correct muscle, or who need encouragement to continue with prescribed treatment. Instruments to provide biofeedback were originally developed by Kegel who used vaginal manometry using an instrument called a perineometer, which measured pressure change occurring during PFM contraction.

Current biofeedback therapy uses either electromyography (EMG) or manometric pressure. EMG measures electrical activity of a muscle in microvolts. The advantage of EMG over manometric pressure is that, provided the machinery is of sufficient sophistication with adequate filtering,

the EMG apparatus can engage the use of the newer types of electrodes that are lightweight and designed to stay in place, hence allowing more functional positions during assessment and treatment. Moreover, EMG can be multichannel, which allows the simultaneous reinforcement of contractions of the PFMs and inhibition of counterproductive accessory muscle contractions (eg, abdominal and gluteal muscle).

Four methods of EMG measurement have been used in the investigation of lower urinary tract dysfunction:

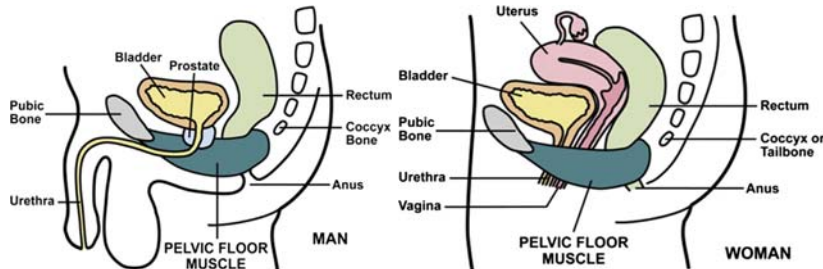
- Vaginal sensor (sEMG)
- Anal sensor or plug electrode (sEMG)
- Skin-surface electrodes (sEMG)
- Needle electrodes

Vaginal and anal electrodes are internal sensors designed to provide a more accurate detection of PFM activity. The accuracy of longitudinal sensing electrodes has been shown to be virtually identical to the gold-standard inserted needle electrodes. However, the use of vaginal or rectal sensors is limited in patients with severe pelvic pain for whom insertion of the sensor causes discomfort,

Patient Guide 3

Pelvic floor muscle exercises

1. What is the Pelvic Muscle? Your pelvic muscle provides support to your bladder and rectum and, in women, the vagina and the uterus. If it weakens, it cannot support these organs and their position can change. This change in position can cause problems with normal function. Keeping the muscle strong can help prevent unwanted urine leakage.
2. Finding the Pelvic Muscle. Without tensing the muscles of your leg, buttocks, or abdomen, imagine that you are trying to control the passing of gas or pinching off a stool. Or imagine you are in an elevator full of people and you feel the urge to pass gas. What do you do? You tighten or pull in the ring of muscle around your rectum: your pelvic muscle. You should feel a lifting sensation in the area around the vagina or a pulling in of your rectum.



3. Exercise Regimen. One exercise consists of both "tightening and relaxing" the muscle. It is equally important to control when your muscle tightens and relaxes. Be sure to relax completely between each muscle tightening.
4. Types of Exercises. There are 2 types of muscle contractions you will need to practice:
 - *Short* (2 seconds): short or quick muscle contractions.
 - Contract or tighten your pelvic muscle quickly and hard, and immediately relax it.
 - *Quick* contractions and *slow* (3 or 5 or 10 seconds) or *long* contractions.
 - Contract or tighten your pelvic muscle and hold for a count of (3 or 5 or 10 as prescribed) seconds, then relax the muscle completely for the same amount of time.
5. Where to Practice. These exercises can be practiced anywhere and anytime. You can do the exercises in these positions:
 - *Lying down*: Lie on your back, flat or with your head on a pillow, knees bent and feet slightly apart. It is helpful to support your knees with a pillow.
 - *Sitting*: Sit upright in a firm seat and straight-backed chair, knees slightly apart, feet flat on the floor or legs stretched out in front and crossed at the ankles.
 - *Standing*: Stand by a chair, knees slightly bent with feet a shoulder-width apart and toes slightly pointed outward. You can also lean on the kitchen counter with your hips flexed.
6. Times to Use the Muscle. If you experience urine loss in one specific position only, like when you stand, then follow these steps:
 - Increase the number of exercises for that position only, or
 - Add additional exercises per day with focus on doing all the exercises in that position only.
7. Common Mistakes.
 - Concentrate and tighten only the pelvic floor muscle. DO NOT tighten thighs, buttocks, or stomach. If you feel your stomach move, then you are also using these muscles.
 - DO NOT hold your breath. Breathe normally and/or count out loud.

8. Can They be Harmful? No, these exercises cannot harm you in any way. You should find them easy and relaxing. If you get back or stomach pain after you exercise, you are probably trying too hard and using your stomach muscles. If you experience headaches, then you are also tensing your chest muscles and probably holding your breath.

9. When Will I See a Change? After 4 to 6 weeks of daily exercise, you will begin to notice less urine leakage. Make the exercises part of your daily lifestyle. Tighten the muscle when you walk, as you stand up, and on the way to the bathroom.

pregnant patients, those who have undergone recent pelvic or rectal surgery, patients with atrophic vaginitis, and patients who would prefer not to have a device inserted internally. Skin-surface electrodes are relatively noninvasive and well tolerated, and provide qualitative information about muscle activity. Needle electrodes are sometimes used during urodynamic testing. The EMG data are measured in microvolts. The actual threshold of PFM required for maintaining continence is unknown at this time, as are the normal values for PFM strength.

At present, there are sophisticated computerized EMG biofeedback units for muscle evaluation and training (Fig. 4), which serve as a diagnostic tool for the clinician while providing visual or auditory feedback to the patient. The baseline and all follow-up EMG recordings should include 2 sets of measurements of maximum or “short/quick” muscle contractions of 2 seconds’ duration with an equal amount of resting muscle activity, and sustained or “long” muscle contractions (5, 10, or 30 seconds) with resting muscle activity for the same length of

Box 6

Exercise prescription sample

Please complete the following exercises:

1. Short Quick Exercise

Contract the muscle Quickly 1 to 2 seconds and immediately relax

2. Long Sustained Exercise:

Contract the muscle, and hold the contraction for a count of 10 then immediately relax for a count of 10

3. Be sure to rest your muscle after each muscle contraction for the same length of the contraction or longer

4. When you have completed both types of exercises in all 3 positions, you will have completed one session

Exercise Session

Lying Down

Do 10 exercises holding for 2 seconds

Do 10 exercises holding for 10 seconds

Sitting

Do 10 exercises holding for 2 seconds

Do 10 exercises holding for 10 seconds

Standing

Do 10 exercises holding for 2 seconds

Do 10 exercises holding for 10 seconds

Do 2 exercise sessions each day, 1 in the morning and 1 in the evening, for a total of 120 exercises

Special Tips:

Always empty your bladder before beginning your exercise session.

Count out loud with sustained or long exercises; remember to keep breathing!

Keep your stomach, leg, and buttock muscles relaxed. Rest your hand on your stomach, it should not move or tense.

If it helps, take a deep breath between each exercise to help you keep other muscles relaxed.

Table 3
Evidence base for PFMT in men undergoing surgery for prostate cancer

Authors, ^{Ref.} Year	N	Intervention	Definition of Continence	Percent Continent: Intervention vs Control Group (%)		
				3 mo	6 mo	1 y
Filocamo et al, ⁶⁹ 2005	300	PFMT taught with digital anal examination in 3 postoperative sessions, home exercise program, bladder control strategies, the “knack” vs usual care	Pad test, number pads used; Dry on ICS-Male Questionnaire	23 vs 14	77 vs 32	89 vs 68
Burgio et al, ⁷⁰ 2006	125	Single session of preoperative biofeedback-assisted PFMT and home exercises vs usual care	No leakage reported in bladder diary	48 vs 32	68 vs 48	
Mariotti et al, ⁷¹ 2009	60	PFMT via biofeedback and electrical stimulation twice a week for 6 wk postoperatively vs usual care	≤2 g on 24-h pad test and no pad use	80 vs 33	97 vs 67	97 vs 97
Ribeiro et al, ⁷² 2010	73	Biofeedback-assisted PFMT weekly plus home exercises × 3 mo or until continent vs brief verbal instructions	No pad use	73 vs 39	88 vs 64	96 vs 75
Tienforti et al, ⁷³ 2012	32	Preoperative biofeedback-assisted PFMT, monthly postoperative biofeedback-assisted PFMT vs verbal and written instructions for home exercises	Score of 0 on the ICIQ-SF	50 vs 6	63 vs 6	

Abbreviations: ICIQ-SF, International Consultation on Incontinence Questionnaire, short form; ICS, International Continence Society.

Data from Refs.^{69–73}

time as the muscle contraction. The ability to relax one's pelvic muscle following a contraction is of utmost importance if one is to gain control and coordination of these muscles.

Manometry is the use of an instrument to detect, assess, and record pressure, and consists of a vaginal or rectal probe with a tube connected to a manometer. The pressure changes can be

measured in centimeters of water (cm H₂O) or millimeters of mercury (mm Hg). Although manometry and pressure sensors are available with certain clinical systems and have been used in several clinical trials, they are primarily used for the treatment of rectal dysfunction.

Research in both men and women is extensive, detailing the efficacy of the use of



Fig. 4. Prometheus biofeedback equipment.

biofeedback-assisted behavioral therapy for PFMT (see [Table 3](#)). However, there is debate over the use of adjuncts such as biofeedback therapy.⁷⁴ The consensus is that conservative therapy combining lifestyle changes, toileting or bladder retraining programs, and PFMT with or without biofeedback are most effective when provided by a clinician who specializes in the area of pelvic floor dysfunction. Clinician-supervised PFMT with biofeedback is considered to provide the most favorable long-term results,¹ and a multidisciplinary Bladder and Pelvic Floor Disorder Center in urology practice provides this service.

BEHAVIORAL TREATMENT COMBINED WITH DRUG THERAPY

Augmenting drug therapy with a supervised BT program is thought to yield the best outcomes in the treatment of UUI and overactive bladder in women,^{1,75–77} may be appropriate in men,⁷⁸ and can be effective when combined with an α -blocker in men with nocturia.⁷⁹ Usually specific medications are prescribed depending on the predominant symptoms. The Urinary Incontinence Treatment Network BE-DRI study by Burgio and colleagues⁷⁶ evaluated whether combined antimuscarinic therapy with behavioral therapy would increase the number of women who could discontinue drug therapy while sustaining a significant reduction in UUI. Although the addition of behavioral therapy did not improve discontinuation of drug therapy, the study found that the combination of behavioral training and drug therapy yielded improved urinary outcomes compared with drug therapy alone.

STIMULATION

E-stim is the application of a low level of electrical stimulation to the PFMs to cause the muscle to

contract. E-stim has a twofold action: contraction of PFMs and inhibition of unwanted detrusor contractions. E-stim is usually a component of a urologic behavioral treatment service, and may be prescribed as a home program using a battery-operated home unit. Patients with LUTS secondary to neurologic disease (eg, multiple sclerosis) may benefit from this therapy. Many clinicians institute this treatment in patients who have failed other behavioral treatments.

Patients with urgency and frequency, and who have been unsuccessful with both drug and behavioral therapy, are considered refractory. Posterior tibial nerve stimulation (PTNS) would be indicated in these patients, and is usually a treatment provided by a Bladder and Pelvic Disorders service. The posterior tibial nerve is a branch of the sciatic nerve (L4–S3 nerve roots) and provides innervation to the posterior leg and foot to cause plantar flexion. Although the exact mechanism is unclear, PTNS is thought to work on afferent pathways to activate inhibitory neurons through a direct sacral route. Tibial nerve stimulation is delivered via a 34-gauge needle electrode inserted 3 to 4 cm above the medial malleolus, the medial aspect of the fibula. Stimulation is delivered over 30 minutes, and treatments are performed weekly for 12 weeks. PTNS has been shown to decrease urgency and frequency.

SUMMARY

There are several possible treatments for UI currently available, and for some a combination of several treatment options may be the most successful. Behavioral interventions are usually preferred, as they are noninvasive and low risk. These treatments are indicated for men and women with LUTS, the majority population seen in urology practices. Evidence-based research has shown these interventions to be effective in decreasing LUTS. Specialized services in this practice setting that offer all behavioral treatments and use nurse practitioners and physician assistants are necessary, and constitute a growth service area in urology. The fastest-growing segment of patients seen in urology have pelvic floor disorders. A multidisciplinary approach that includes surgical and nonsurgical treatments is required.

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Office-Based Ultrasound for the Urologist

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KEYWORDS

- Office ultrasonography • Renal ultrasonography • Bladder ultrasonography
- Scrotal ultrasonography • Penile Doppler ultrasonography • Prostate ultrasonography

KEY POINTS

- Renal ultrasonography allows assessment of a dilated upper urinary tract particularly in pediatric patients, assessment of flank pain during pregnancy, and evaluation of hematuria in patients who are not candidates for intravenous pyelography, contrast computed tomography, or magnetic resonance imaging.
- Bladder ultrasonography allows assessment of postvoid residual in male patients with benign prostatic hyperplasia, particularly during the initial workup.
- Scrotal ultrasonography allows assessment of a scrotal or testicular mass or swelling, assessment of acute scrotal pain, and assessment of male infertility.
- Penile Doppler ultrasonography allows assessment of the cavernosal arteries and their spectral waveform evolution following intracavernosal injection of a pharmacostimulant in patients with erectile dysfunction.
- Transrectal ultrasound of the prostate is the most common modality for imaging the prostate during biopsy; new modalities include color Doppler prostate ultrasonography, three-dimensional ultrasonography, and elastography of the prostate.

INTRODUCTION

Ultrasonography provides the busy office urologist with a minimally invasive, low-risk imaging modality that is easily accessible in the clinic setting. The basic concepts behind ultrasound imaging involve using a frequency (number of sound waves per second, measured in *hertz* [Hz]) too high for the human ear to hear.¹ Ultrasound waves are generated by a transducer, which is housed in an ultrasound probe that is shaped for the desired application. These waves are then transmitted to the tissue of interest and waves that reflect (or echo) after bouncing off the tissue of interest are incorporated by a receiving element in the transducer. Through a process called acoustic-

electric conversion, the transducer transforms the sound energy into electrical energy, which is processed by the ultrasound console computer to generate white pixels corresponding to returning signals displayed on a black background.² This article reviews the basic applications of ultrasound imaging in the office setting, including renal, bladder, scrotal, penile Doppler, and prostate ultrasonography.

RENAL ULTRASONOGRAPHY

Given a urologist's knowledge of the anatomy of the kidney and retroperitoneum, performing a focused retroperitoneal ultrasound in the office setting can be useful for specific clinical

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indications. The ultrasound probe and transducer for renal ultrasonography is a 3.5- to 5.0-MHz curved probe; a 6- to 10-MHz transducer may be used for pediatric patients.³ The patient is placed in the supine position and scanning begins in the midclavicular line for the kidney of interest. In the sagittal plane, the probe is moved laterally until a midsagittal view of the kidney is obtained; when analyzing the image, the upper pole of the kidney is located on the left side of the monitor (**Fig. 1**). Imaging of the kidney in the transverse plane is possible by rotating the probe 90° counterclockwise and the kidney is scanned from upper to lower pole. Important office-based indications for renal ultrasound include follow-up of hydronephrosis on prenatal ultrasound, assessment of a dilated upper urinary tract particularly in pediatric patients, assessment of flank pain and monitoring ureteral stent position during pregnancy, and evaluation of hematuria in patients who are not candidates for intravenous pyelography (IVP), contrast computed tomography (CT), or magnetic resonance imaging (MRI).³

Pediatric patients requiring renal imaging represent an important subset of patients for which renal ultrasonography is used. Postoperative follow-up of pediatric patients following ureteroscopic treatment of lithiasis is effective with ultrasound. Resorlu and colleagues⁴ found negative and positive predictive values of 97.7% and 100%, respectively, for detecting hydronephrosis at 3 months postoperatively for ureteroscopic manipulation of lithiasis. Similar to postureteroscopy upper tract surveillance, ultrasound is important for surveillance of postpyeloplasty patients and can be used to identify patients who may require a mercaptoacetyltriglycine-3 scan in the setting of postoperative deteriorating renal function.⁵

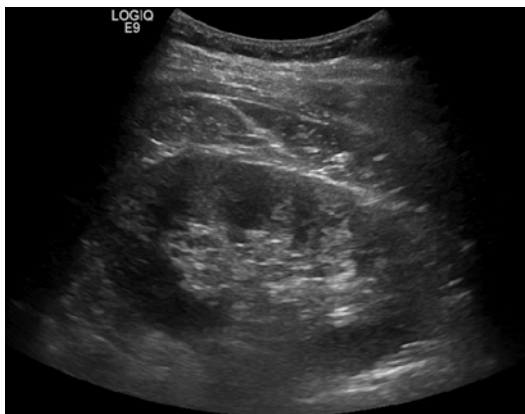


Fig. 1. Normal renal ultrasonography: left kidney measuring 10.8 cm in length demonstrating isochoic parenchymal echogenicity.

Recently, 3-dimensional (3D) ultrasonography has been reported when evaluating pediatric patients. 3D ultrasonography improves visualization of complex anatomy and pathologic condition in any plane and allows evaluation of a dilated collecting system with similar specificity to IVP and MR urography.⁶

When assessing a pregnant patient with renal colic, determining whether this is secondary to physiologic hydronephrosis or lithiasis may be challenging. In experienced hands, ultrasonography has a sensitivity of greater than 95% for diagnosis of nephrolithiasis.⁷ A review of 300 pregnant patients presenting with renal colic by Andreoli and MacMahon⁸ found that the accuracy of ultrasonography for predicting a calculus improved from 56.2% to 71.9% when features of obstruction were present, such as the absence of a ureteric jet and an elevated resistive index. Although recent studies have suggested that low-dose CT scan may be safe and improve the efficacy of lithiasis diagnosis in pregnant patients,⁹ ultrasound remains an important and safe modality for diagnosing nephrolithiasis and monitoring progression of stone passage.

As part of the evaluation for hematuria, the upper urinary tract has historically been evaluated with an IVP and more recently a contrast CT or MRI of the abdomen and pelvis. In patients with an elevated creatinine, a contrasted study risks further worsening of kidney function providing an opportunity for ultrasonography to evaluate the upper urinary tract. In this subset of patients, ultrasonography offers the ability to detect renal masses and cysts (**Fig. 2**). Mucksavage and colleagues¹⁰ analyzed 116 patients who underwent

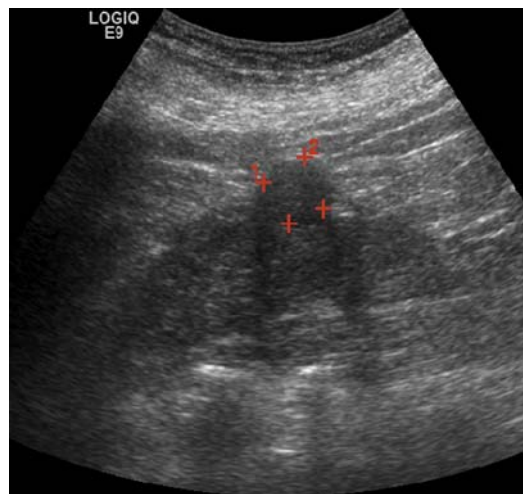


Fig. 2. Renal ultrasonography demonstrating a right 1.72 × 1.80 × 1.78 cm interpolated solid mass (delineated by red +).

ultrasound prior to imaging before definitive therapy. Patients also received an MRI or CT scan and they found that the size differences between CT and MRI compared with ultrasound was less than 3.5% and ultrasound correlated well with both MRI and CT (both $P < .001$). However, diagnosis of upper tract transitional cell carcinoma with ultrasonography is difficult to differentiate from other causes of filling defects of the renal collecting system, such as fungus balls or sloughed papillae.¹¹ Ultrasound should not replace an IVP or contrasted CT or MRI for the evaluation of the upper urinary tract in the setting of hematuria; however, in select patients with poor kidney function it may be considered a safe alternative.

BLADDER ULTRASONOGRAPHY

Bladder ultrasonography is an important tool for the office urologist, allowing evaluation of the lower urinary tract and prostate in men and the bladder in women. A curved probe set at 3.5 to 5 MHz is used with the patient in the supine position.³ The bladder should be viewed in the transverse and sagittal planes, angling the probe beneath the pubic bone for optimal bladder assessment (**Fig. 3**). Arguably the most common utilization of bladder ultrasonography in the office setting is assessment of postvoid residual (PVR) in male patients with benign prostatic hyperplasia (BPH). Although the utility of PVR as an objective measure for BPH treatment efficacy and as an indicator for surgical treatment have been



Fig. 3. Sagittal view of the bladder and prostate. The median lobe of the prostate extends into the bladder. (From Fulgham PF, Bishoff JT. Urinary tract imaging: basic principles. In: Wein AJ, Kavoussi LR, Novick AC, editors. Campbell-Walsh urology. 10th edition. Philadelphia: Elsevier/Saunders; 2012. p. 122; with permission.)

inconclusive,¹² it is generally accepted that PVR volume be included in the initial assessment of a patient with BPH and during monitoring of patients undergoing conservative treatment regimens.¹³ Additional indications for bladder ultrasonography in the office setting may include evaluation of bladder wall configuration and thickness, detection of ureteroceles, assessment for ureteral obstruction, detection of perivesical fluid collections, evaluation of clot retention, confirmation of catheter position, and guidance of suprapubic tube placement.³

SCROTAL ULTRASONOGRAPHY

Scrotal ultrasonography provides the urologist with high-quality images when evaluating patients with acute scrotal pain, a palpable scrotal mass, or an enlarged scrotum on physical examination. Ultrasonography is typically performed with high frequency (6–12 MHz) and a 4- or 7.5-cm linear array transducer.³ Patients should be in the supine position with the scrotum supported by a towel. The penis should be out of the way and adequate conducting gel should be used to circumvent artifact that may result secondary to scrotal hair. Transverse and sagittal images should be obtained paying particular attention to each testis, epididymis, and spermatic cord (**Fig. 4A**). The 2 testes should be compared for echogenicity because certain infiltrative processes (eg, leukemic testicular involvement) may result in subtle changes that are only noticeable when a bilateral comparison is used. Furthermore, Doppler ultrasonography should be used to determine blood flow to each testis particularly when clinical suspicion is concerning for testicular torsion. Indications for in-office scrotal ultrasonography include assessment of a scrotal or testicular mass or swelling, assessment of acute scrotal pain, and assessment of male infertility.

Ultrasonography of the scrotum in the setting of a swollen scrotum or a palpable testis mass allows for delineation between extratesticular (eg, hydrocele) (see **Fig. 4B**) and intratesticular (eg, tumor, infection) causes (see **Fig. 4C**). For medicolegal reasons, evaluation for malignancy should also include a review of the images by a radiologist. Micalef and colleagues¹⁴ retrospectively analyzed 256 patients for scrotal swelling and reported that 75% of cases involved extratesticular causes (most commonly hydrocele) and 25% involved intratesticular causes, most commonly secondary to infection (50%) and tumor (21%). Color Doppler ultrasonography of a testicular nodule is characterized by hypervascularity with irregular branching patterns.¹⁵ Leydig cell tumors often have a unique

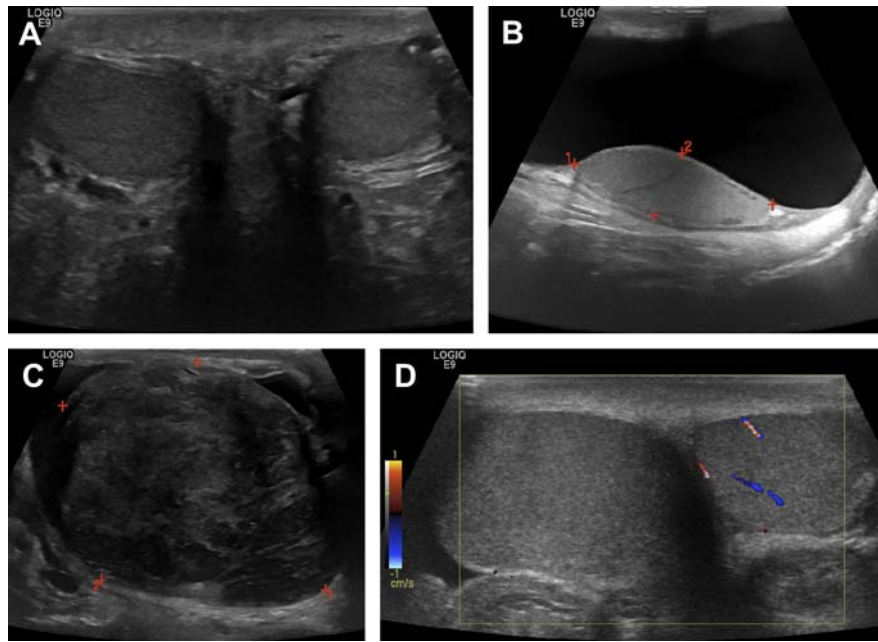


Fig. 4. Scrotal ultrasonography. (A) Midtransverse image of left and right testis demonstrating heterogeneous parenchymal echogenicity. (B) Sagittal image demonstrating a $5.5 \times 1.8 \times 3.3$ cm left testis (delineated by red +) and surrounding $9.1 \times 5.5 \times 6.2$ cm hydrocele. (C) Sagittal image demonstrating a $6.5 \times 4.8 \times 4.9$ cm right testis tumor encompassing the entire right testis (delineated by red +). (D) Midtransverse image demonstrating normal flow to the left testis and acute right testicular torsion.

ultrasound finding of hypoechoic nodules with peripheral hypervascularity and no internal flow.¹⁶ When a hydrocele is suspected on physical examination (no nodules, nonpalpable testis, scrotal swelling), ultrasonography may be used to confirm the diagnosis, demonstrating an increased fluid volume around the testis and in increased pulsatility index.

The assessment of the acute scrotum relies on an accurate history and physical examination and, if needed, ultrasonography. Clinical suspicion for testicular torsion obviating scrotal exploration should not be delayed because of ultrasonographic confirmation. The hallmark of testicular torsion on ultrasonography is the absence of intratesticular blood flow (see Fig. 4D); paratesticular blood flow secondary to collateral circulation may appear within hours of testicular torsion.³ Although the paradigm at many tertiary centers is to explore an acute scrotum regardless of ultrasonographic findings for fear of overlooking testicular torsion, a recent report by Altinkilic and colleagues¹⁷ suggests that normal intratesticular perfusion using color-coded duplex sonography (CCDS) obviates scrotal exploration. The authors assessed the diagnostic value of CCDS in 236 patients (median age 13 years) with clinical suspicion of testicular torsion who subsequently underwent exploration whereby

the surgeon was blinded to the ultrasound findings. Testicular torsion was the most common cause of acute scrotum (50.4%), followed by torsion of the testicular appendage (34.8%) and epididymo-orchitis (7.6%). The reported sensitivity, specificity, and positive and negative predictive values of detecting testicular torsion with CCDS were 100%, 75%, 80%, and 100%, respectively.¹⁷

Scrotal ultrasonography may elucidate pathologic conditions affecting male fertility, including a varicocele (Fig. 5), which is the most common abnormality in infertile men with abnormal semen analysis. The degree of testicular size difference that may warrant surgical repair in infertile men has not been defined; however, a 20% size discrepancy has been proposed as a threshold for intervention.¹⁸ Although varicocele is often diagnosed on physical examination of the testis and spermatic cord, accuracy of palpation may be subjective. Pierik and colleagues¹⁹ analyzed 1372 infertile men who were assessed with color Doppler ultrasonography and found a scrotal abnormality in 38% of men. Varicocele (29.7%) was the most common abnormality, followed by epididymal cyst (7.6%), hydrocele (3.2%), testicular microlithiasis (0.9%), testicular cyst (0.7%), and testicular tumor (0.5%). Interestingly, 67% and 60% of overall sonographic findings and

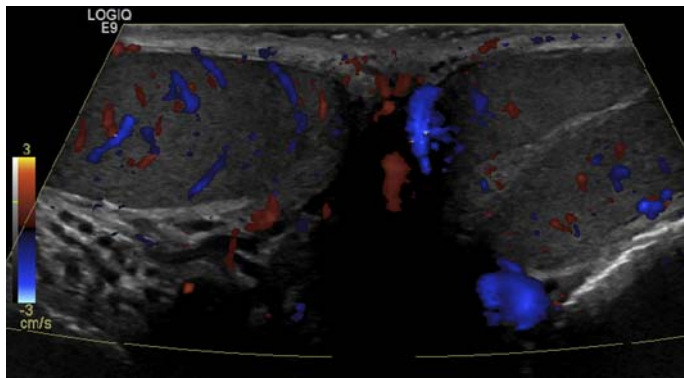


Fig. 5. Midtransverse scrotal ultrasonography demonstrating a large left varicocele.

varicoceles, respectively, were not evident on physical examination.¹⁹

PENILE DOPPLER ULTRASONOGRAPHY

Penile Doppler ultrasonography allows assessment of the cavernosal arteries and their spectral waveform evolution following intracavernosal injection of a pharmacostimulant in patients with erectile dysfunction (ED).^{20–23} Depending on the institution, this may be performed in the office setting or by an ultrasound technician in a radiology suite, with subsequent interpretation of results by an urologist. In the authors' experience, the patient is brought to the radiology suite and a 1 mL injection of an alprostadil-papaverine-phentolamine mix using a 25-gauge needle is performed. The injection is made in either corpora cavernosa at the 3- or 9-o'clock position at the base of the penis. Following injection, a linear transducer set at 7 MHz or higher is used; scanning is typically performed on the ventral surface of the penis; however, the dorsal and lateral surfaces may be used if necessary.^{23,24} Images and waveforms are obtained in both the longitudinal and the transverse planes from the base of the penis to the tip of the glans. Attention to the cavernosal arteries, integrity of the corpus cavernosa, and identification of plaques, tumors, and calcifications is important. Color Doppler ultrasonography is necessary for measuring the systolic velocity in the cavernosal arteries and for determining the preinjection (**Fig. 6A**) and postinjection diameters (see **Fig. 6B**) of the arteries. The thresholds for normal systolic and diastolic velocities of blood flow relating to the cavernosal arteries following injection of a pharmacostimulant are generally regarded as a peak systolic velocity (PSV) of greater than 25 to 35 cm/s and an end diastolic velocity (EDV) of less than 5 to 7 cm/s (see **Fig. 6C**).^{20–23,25}

Arterial disease is one of the most common causes of ED with common predisposing factors including hypertension, diabetes mellitus, obesity, dyslipidemia, smoking, and a sedentary lifestyle.^{26,27} A PSV of less than 25 cm/s has been associated with a strong likelihood of severe arterial disease. A second cause of ED includes venous incompetence, or the finding of persistent diastolic flow and elevated EDV; an EDV greater than 5 to 7 cm/s is highly suggestive of a venous leak.²⁵ Third, penile Doppler ultrasonographic evaluation has been used in the diagnosis and treatment of Peyronie disease (PD), a benign, localized connective tissue disorder of unknown cause that causes fibrous thickening of the penile tunica albuginea. This fibrous thickening often leads to painful erections and erectile deformities. Evaluation in patients with PD provides an anatomic evaluation of the penile deformity and may identify concomitant ED, as ED has been associated with PD in as many as 80% of patients.²⁸ Chung and colleagues²⁹ evaluated 1500 men with ED over a 10-year period with penile Doppler ultrasonography, of which 891 men presented with PD and 609 men had ED. The authors found that men with ED had higher rates of diabetes and coronary artery disease; patients with impaired cavernosal arterial flow was observed in men with decreased penile rigidity and penile pain, and men with a higher EDV was associated with men having difficulty maintaining an erection and tunical thickening.

An underreported use of penile Doppler ultrasonography is for men with ED following a prostatectomy or cystectomy. Hekal and colleagues³⁰ evaluated 45 male patients with penile Doppler ultrasonography who had a cystectomy, including 21 patients with nerve-sparing technique and 24 patients with non-nerve-sparing technique over the course of 12 months postoperatively. PSVs were comparable between the 2 groups during

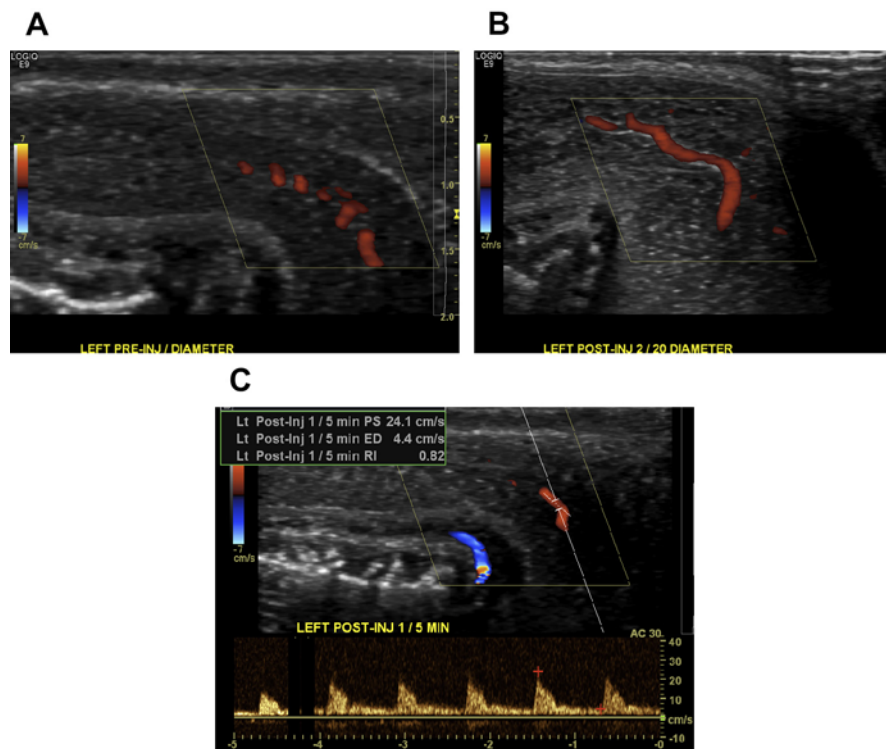


Fig. 6. Penile Doppler ultrasonography. (A) Prepharmacostimulant injection measurement of the left cavernosal artery diameter. (B) Postinjection measurement of the left cavernosal artery diameter. (C) Doppler ultrasonographic measurement of the PSV (red, 24.1 cm/s) and EDV (blue, 4.4 cm/s).

follow-up. EDV significantly deteriorated postoperatively compared to preoperative evaluation in both groups; however, gradual improvement in EDV was seen in the nerve-sparing group 12 months after surgery. Kawanishi and colleagues³¹ evaluated 123 male patients with localized prostate cancer with penile Doppler ultrasonography before and after prostatectomy and found that 21 patients (17%) had normal erectile function before surgery and 9 (43%) of the 21 potent men had potency 4 to 6 weeks postoperatively. Finally, Ohebshalom and colleagues³² analyzed 111 men with normal erectile function preoperatively within 6 months of prostatectomy with penile Doppler ultrasonography and found 32 patients (29%) had normal erectile hemodynamics after prostatectomy. In this cohort, 12 patients (11%) had a venous leak. When comparing patients with normal to those with abnormal hemodynamics, the mean International Index of Erectile Function scores were 25 and 17 ($P = .025$); the percentage of patients with functional erections for sexual activity without pharmacologic agents was 47% versus 22% ($P = .018$) and the percentage of patients responding to sildenafil citrate was 72% versus 43% ($P = .03$).³²

PROSTATE ULTRASONOGRAPHY

Transrectal ultrasound (TRUS) of the prostate was first described in 1968 by Watanabe and colleagues,³³ and with expanded technology led to the first TRUS-guided sextant prostate biopsy by Hodge and colleagues³⁴ in 1989. TRUS is now used by most urologists to direct prostate biopsies accurately; although it cannot reliably detect prostate cancer, it is an inexpensive modality for imaging the prostate. In general, the patient is provided with either 3 days of a perioperative oral fluoroquinolone (eg, Ciprofloxacin) or a single-dose aminoglycoside (eg, Gentamicin) administered on the day of biopsy. A Fleet's enema may be self-administered by the patient on the day of the biopsy. On the office procedure table, the patient is placed in the left lateral decubitus position with the buttock positioned slightly over the side of the table to allow adequate mobility of the transrectal ultrasound probe. With the patient appropriately positioned and draped, a digital rectal examination should be performed to assess for size, induration, nodules, and/or hypertrophy of the prostate gland. The rectal ultrasound probe, with adequate lubrication, is then slowly inserted into the rectum.

TRUS of the prostate is generally performed at very high frequencies of 5 to 10 MHz, much higher than imaging of other urologic structures (Fig. 7).² The echogenicity of structures within the prostate gland are compared relative to the medium-gray echogenicity of the peripheral zone—structures that are the same echogenicity are isoechoic: those that are brighter are hyperechoic and those that are darker are hypoechoic.² Peripheral zone palpable prostatic adenocarcinomas (PCa) typically are hypoechoic^{35,36}; however, most nonpalpable peripheral zone cancers do not demonstrate abnormal echo patterns. Transition zone tumors are even more isoechoic than peripheral zone cancers.² Following a general surveillance of the prostate assessing for these abnormalities, a measurement of the prostate in 3D is obtained to provide an accurate prostate volume. A local prostatic block is achieved using 1% lidocaine through a long spinal needle (eg, 7-inch, 22-gauge) using TRUS guidance along the biopsy channel of the transducer. Multiple techniques for injecting local anesthetic have been described and a common technique is to identify the level of the seminal vesicles near the bladder base at the junction of the seminal vesicles and prostate and to inject 5 mL lidocaine bilaterally.³⁷

A biopsy gun or spring-driven, 18-gauge, needle core biopsy device is passed through the guide attached to the ultrasound probe and prostate biopsies are performed sequentially in this manner.³⁷ In the authors' experience, a 12-core, double sextant, biopsy is performed in either the transverse or the sagittal plane: 2 cores from each side of the prostate base, mid-gland and apex, are obtained. Numerous studies over the past 20 years have advocated for an extended core biopsy template over the traditional sextant biopsy. In 2000, Presti and colleagues³⁸ analyzed 483 patients in a prospective study and found that PCa detection rate increased from 80% to 96% when adding lateral cores from the base and mid gland.³⁹ Uno and colleagues⁴⁰ analyzed

313 patients who underwent TRUS-guided 14-core biopsy (standard 6 biopsy cores, 6 lateral cores, and 2 transition zone cores) and found 127 patients (40.6%) with PCa, 28 (22%) patients of which PCa would not have been detected by the sextant method alone. Depending on local guidelines, biopsy samples are placed in 10% formalin containers and sent to the pathology laboratory. After completing the biopsy, digital rectal pressure with gauze is sustained until adequate rectal hemostasis is achieved.

Office-based TRUS-guided prostate biopsy may be associated with considerable pain and anxiety for the patient. Although the procedure is most often only associated with minor complications, the patient's perception of the procedure may be traumatic and worrisome. Zisman and colleagues⁴¹ prospectively enrolled 211 men undergoing TRUS-guided prostate biopsy in a study focusing on pain, anxiety, and ED associated with the procedure. They reported that 20% of patients reported pain during the procedure, which correlated with pain in the first 24 hours after biopsy. Inflammatory changes on biopsy and a younger patient correlated with persistent pain at 2 and 7 days after biopsy. Sixty-four percent of patients reported prebiopsy anxiety and this correlated with pain during the biopsy. ED was reported in 15% of previously potent men at 7 and 30 days postbiopsy.⁴¹

Given the level of anxiety and pain that may be associated with office-based TRUS-guided prostate biopsy, significant resources have been allocated to elucidating appropriate analgesia during the procedure. Ozden and colleagues⁴² performed a prospective, randomized, placebo-controlled study analyzing the dose and injection location for periprostatic nerve block in 175 men. Seven groups of 25 men were allocated to receive 5 mL saline or 2.5, 5, or 10 mL 1% lidocaine injected at the prostate base or base and apical location. The authors reported that 10 mL local anesthetic injections provided better analgesia irrespective

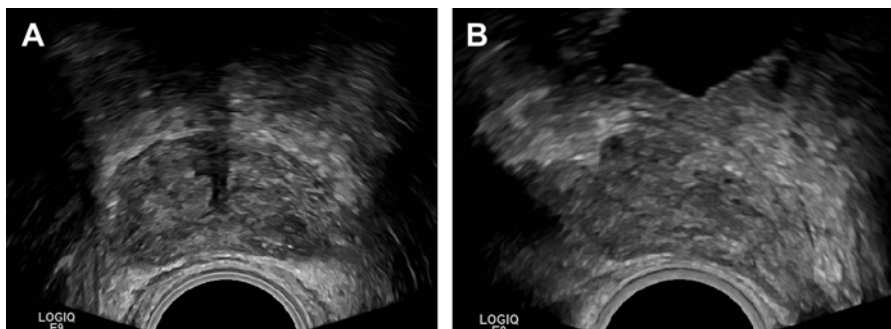


Fig. 7. Normal transrectal ultrasonography of the prostate in the (A) transverse and (B) sagittal planes.

of location.⁴² Seckiner and colleagues⁴³ performed a prospective, randomized-controlled study comparing lidocaine and tramadol for periprostatic nerve blockage during TRUS-guided prostate biopsy in 90 patients. Group 1 (n = 30) received lidocaine; group 2 (n = 29) received tramadol, and group 3 (n = 31) received saline injection. Subsequently, visual pain scales were used to rate the patient's pain at 10 minutes postbiopsy; the mean pain scores of lidocaine, tramadol, and placebo groups were 1.73, 2.89, and 4.32 ($P < .01$), respectively, suggesting that tramadol may be as effective as lidocaine for providing biopsy analgesia. Meta-analyses advocate the use of adequate analgesia, primarily lidocaine, during TRUS-guided prostate biopsy.^{44,45}

Modifications to the traditional gray-scale sonography have recently been developed, including color Doppler (Fig. 8A) and power Doppler

ultrasound (see Fig. 8B). Color Doppler ultrasonography depicts the velocity of blood flow in a directionally dependent manner and power Doppler imaging uses amplitude shift to detect both flow and velocity.³⁷ These advanced techniques to aid in ultrasound detection of PCa were developed because of radical prostatectomy specimens demonstrating increased microvessel density in PCa specimens.⁴⁶ Color and power Doppler ultrasound have unfortunately demonstrated mixed results as early studies' outcomes have not been replicated, demonstrating overall poor sensitivity (13%–86%) secondary to benign pathologic abnormalities also showing ultrasound abnormalities.^{39,47,48} Although outside the scope of the current article, contrast-enhanced agents and techniques have been applied to Doppler ultrasonography to attempt to increase the specificity and sensitivity of targeted ultrasound-guided prostate biopsy.^{39,49,50}

Further advances in prostate ultrasonography include the use of 3D ultrasonography and elastography. 3D-TRUS requires a specialized endocavitary ultrasound probe; this technology allows simultaneous biplanar imaging of the prostate with computer reconstruction providing a coronal plane as well as a 3D image. Hamper and colleagues⁵¹ compared 16 patients undergoing TRUS-guided prostate biopsy with 2-dimensional and 3D ultrasound subjectively reporting an improved ability to visualize hypoechoic lesions in 3D most notably in the coronal view. Furthermore, prostate volume calculations were believed to be more accurate, consistently 20% smaller than traditional dimensional volume calculations. More recent studies have suggested 84% sensitivity and 96% specificity for preoperative 3D ultrasonography detecting macroscopic extracapsular tumor extension of radical prostatectomy specimens.⁵²

PCa is associated with increased cellular density and glandular architecture loss, which may result in a firmness or induration appreciated on digital rectal examination.³⁹ These findings result in a decreased elasticity of the tissue and may be detectable by elastography. This technique uses real-time ultrasonography of the prostate at baseline and under varying degrees of free-hand compression of the ultrasound probe against the prostate tissue. Through computerized calculations, an elastogram of the prostate is obtained, identifying regions with decreased tissue elasticity that may be suggestive of malignancy (Fig. 9). Two recent studies have reported the accuracy of elastography. In 2005, König and colleagues⁵³ analyzed 404 patients who underwent TRUS biopsy with subsequent generation of elastograms.

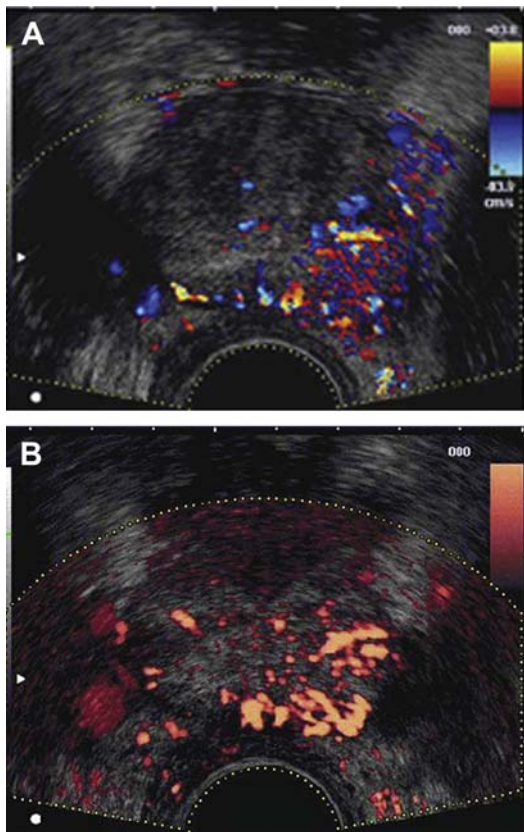


Fig. 8. Color Doppler (A) transrectal ultrasonography (TRUS) and power Doppler (B) TRUS identify a Gleason 4 + 4 = 8 adenocarcinoma in the left midgland (arrow). (From Trabulsi EJ, Halpern EJ, Gomella LG. Ultrasonography and biopsy of the prostate. In: Wein AJ, Kavoussi LR, Novick AC, editors. Campbell-Walsh urology. 10th edition. Philadelphia: Elsevier/Saunders; 2012. p. 2744; with permission.)

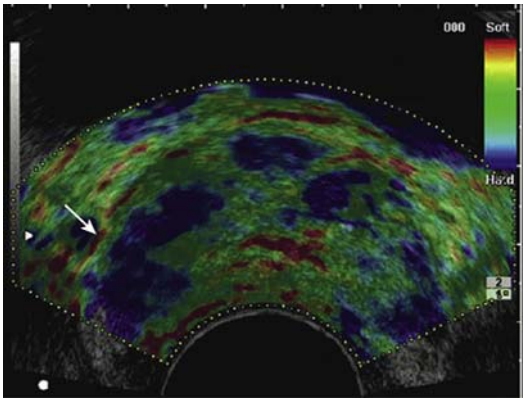


Fig. 9. Elastography demonstrates an area of decreased compliance in the right base consistent with an underlying malignancy (*blue near arrow*). The color scale in the upper right corner indicates relative tissue "firmness." Targeted biopsy of this region revealed a Gleason 4 + 4 = 8 adenocarcinoma. (From Trabulsi EJ, Halpern EJ, Gomella LG. Ultrasonography and biopsy of the prostate. In: Wein AJ, Kavoussi LR, Novick AC, editors. Campbell-Walsh urology. 10th edition. Philadelphia: Elsevier/Saunders; 2012. p. 2746; with permission.)

Of the 151 patients with PCa, 84% of patients had an abnormal elastogram. In 2008, Pallwein and colleagues⁵⁴ analyzed 492 patients who underwent elastography and TRUS biopsy and noted a sensitivity of 86% and specificity of 72% for detection of PCa on elastogram, corresponding to a negative predictive value of 91.4%.

SUMMARY

The use of office-based ultrasound continues to be an undisputable imaging modality for the clinical urologist when assessing the kidneys, bladder, scrotum, erectile function, and prostate. The lack of radiation exposure risk is advantageous to the operator and patient alike. With the advent of color Doppler and 3D ultrasonography, technology continues to evolve and broaden the indications for ultrasonography, ultimately improving patient care. Ultrasonography is increasingly being used in the office setting by urologists providing an imaging modality for initial diagnosis, interventional management, and longitudinal follow-up of urologic diseases.

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